Emergency Use Authorization (EUA) Amendment for an Unapproved Product Review Memorandum

Identifying Information

Application Type	EUA (Event-driven EUA request) Amendment
Application Number	EUA 27034 (Amendment 132)
Sponsor	Pfizer, Inc., on behalf of BioNTech SE
Submission Date	April 9, 2021
Receipt Date	April 9, 2021
Signatory Authority	Marion F. Gruber, Ph.D., Director, CBER/OVRR
Principle Discipline Reviewers from the Review Team	Ramachandra Naik, Ph.D., Chair, OVRR/DVRPA; CAPT Michael Smith, Ph.D., Regulatory Project Manager, OVRR/DVRPA; Laura Gottschalk, Ph.D., Regulatory Project Manager, OVRR/DVRPA; Susan Wollersheim, M.D., Clinical reviewer, OVRR/DVRPA; Lucia Lee, M.D., Clinical reviewer, OVRR/DVRPA Lei Huang, Ph.D., Biostatistics reviewer, OBE/DB; Haruhiko Murata, Ph.D., CMC/Product reviewer, OVRR/DVP; Xiao Wang, Ph.D., CMC/Product reviewer, OVRR/DVP; Kerry Welsh, M.D., Pharmacovigilance reviewer, OBE/DE; Narayan Nair, M.D., Pharmacovigilance reviewer, OBE/DE; Brenda Baldwin, Ph.D., Data Integrity reviewer, OVRR/DVRPA; Bhanumathi Kannan, Ph.D., BIMO reviewer, OCBQ/DIS/BMB; Oluchi Elekwachi, Ph.D., Labeling reviewer, OCBQ/DCM/APLB
Review Completion Date	
Established Name/Other names used during development	Pfizer-BioNTech COVID-19 Vaccine / BNT162b2
Dosage Forms/Strengths and Route of Administration	A 0.3 mL suspension for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 12 years of age and older

Table of Contents

List of Tables

List of Figures

Glossary

AE	adverse event
AESI	adverse event of special interest
BNT162b2	Pfizer-BioNTech COVID-19 Vaccine
CBER	Center for Biologics Evaluation and Research
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
DVRPA	Division of Vaccines and Related Products Applications
DVT	deep vein thrombosis
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GMR	geometric mean ratio
GMT	geometric mean titer
HHS	Health and Human Services
IND	Investigational New Drug (application to the FDA)
MIS-C	multisystem inflammatory syndrome in children
OVRR	Office of Vaccines Research and Review
PE	pulmonary embolism
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
SSRI	selective serotonin reuptake inhibitor
TTS	thrombosis with thrombocytopenia syndrome
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy

1. Executive Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to present an extraordinary challenge to global health and, as of April 30, 2021, has caused more than 155 million cases of COVID-19 and claimed the lives of more than 3.2 million people worldwide. In the United States, more than 32 million cases have been reported to the Centers for Disease Control and Prevention (CDC), of which 1.5 million cases (4.7%) were among individuals 11 to 17 years of age. Based on a declaration by the Secretary of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an Emergency Use Authorization (EUA) for a COVID-19 vaccine after determining that certain statutory requirements are met.

On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 Vaccine (also known as BNT162b2, an mRNA vaccine encoding the SARS-CoV-2 spike glycoprotein and administered as a 2-dose regimen 21 days apart) for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. Issuance of the EUA was based on a finding of vaccine efficacy (VE) of 95% compared to placebo against confirmed COVID-19 at least 7 days after completion of the 2-dose vaccination regimen in a study of approximately 44,000 participants, with a highly favorable benefit/risk balance based on assessment of adverse events in a safety population of approximately 38,000 study participants with a median follow-up of 2 months after completion of the vaccination regimen. On April 9, 2021, the Sponsor (Pfizer, on behalf of Pfizer and BioNTech) submitted a request to amend the EUA to include use in individuals 12 through 15 years of age (abbreviated 12-15 years). The EUA amendment request includes safety and effectiveness data from the ongoing Phase 2/3 randomized, double-blinded and placebo-controlled trial of the Pfizer-BioNTech COVID-19 Vaccine in 2,260 participants 12-15 years of age.

Vaccine effectiveness in the adolescent age group was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers (SARS-CoV-2 mNG microneutralization assay) at 1 month after Dose 2 in participants 12-15 years of age with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE has been demonstrated). Although a specific level of neutralizing antibodies has not been established to correlate with protection, and other aspects of the immune response elicited by the vaccine may also be important, available clinical and non-clinical data support use of neutralizing antibody responses as a clinically relevant immune biomarker for inferring effectiveness through immunobridging in this specific setting. In the planned immunobridging analysis, the geometric mean ratio (GMR) of neutralizing antibody titers (adolescents to young adults) was 1.76 (95% CI: 1.47, 2.10), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). In a descriptive immunogenicity analysis, seroresponse rates among participants without prior evidence of SARS-CoV-2 infection were seen in 97.9% of adolescents and 100% of young adults (difference in seroconversion rates: -2.1%; 95% CI: -6.0%, 0.9%). Immunogenicity outcomes were consistent across demographic subgroups, such as baseline SARS-CoV-2 status, comorbidities, ethnicity, race and sex. In the supplemental efficacy analysis, VE after 7 days post Dose 2 was 100% (95% CI 75.3; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% in the group of participants with or without prior infection. VE between Dose 1 and Dose 2 was 75.0% (95% CI 7.4; 95.5), with divergence of cumulative incidence of COVID-19 cases in BNT162b2 vs. placebo groups beginning at approximately 14 days after Dose 1. Although based on a small number of cases in descriptive analyses, the supplementary VE data provide compelling direct evidence of clinical benefit in addition to the immunobridging data.

Safety data from a total of 2,260 adolescents 12-15 years of age randomized to receive vaccine (N=1,131) or placebo (N=1,129) with a median of greater than 2 months of follow-up after the second dose suggest a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. The most common solicited adverse reactions after any dose included injection site pain (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), all of which were generally mild to moderate and lasted a few days. Severe solicited local adverse reactions and systemic adverse events occurred in up to 2.4% of 12-15-year-old BNT162b2 recipients, were more frequent after Dose 2 (most common: fatigue 1.3%, headache 1.0%, chills 0.4%) than after Dose 1 (most common: fatigue 2.4%, headache 2.0%, chills 1.8%) and more frequent after any dose in BNT162b2 recipients than age-matched placebo recipients. Among recipients of BNT162b2, severe solicited adverse reactions/events in 12-15-year-olds occurred less frequently than in 16-25-year-olds. No deaths were observed in this age group during the follow-up period. Serious adverse events, while uncommon (<0.5%), represented medical events expected to occur among individuals in this age group and with the underlying conditions represented in the study population, and available data do not suggest a causal relationship to BNT162b2. There were no notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events among study participants 12-15 years of age that would suggest a causal relationship to BNT162b2 vaccine. Review of longer-term safety data from participants 16 years and older enrolled in the ongoing study and safety surveillance data from use of the vaccine under EUA has not raised any safety concerns aside from a documented incidence of anaphylaxis (occurring primarily among individuals with history of severe allergic reaction to other medications or foods) of 0.46 cases per million doses administered, similar to reported rates of anaphylaxis following licensed preventive vaccines.

The review team therefore recommends issuance of an EUA for use of the Pfizer-BioNTech COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health and, as of April 30, 2021, has caused more than 155 million cases of COVID-19 and claimed the lives of more than 3.2 million people worldwide. In the United States, more than 32 million cases and 580,012 deaths have been reported to the CDC. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS, and the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Additional background information on the SARS-CoV-2 virus and COVID-19 pandemic may be found in the December 11, 2020 emergency use authorization (EUA) decision memorandum for the Pfizer-BioNTech COVID-19 vaccine.[1]

Since March 1, 2020, approximately 1.5 million COVID-19 cases in individuals 11 to 17 years of age have been reported to the Centers for Disease Control and Prevention (CDC). [2] Among these cases approximately 9,200 resulted in hospitalization, with more than 600 ICU admissions and more than 200 deaths. It is difficult to estimate the incidence of COVID-19 among children and adolescents because they are frequently asymptomatic and infrequently tested.[3,4] Children

and adolescents appear less susceptible to SARS-CoV-2 infection and have a milder COVID-19 disease course as compared with adults.[5,6] However, because adolescents and adults have similar SARS-CoV-2 viral loads in their nasopharynx, adolescents may play a role in community transmission.[7,8] Transmission of SARS-CoV-2 in school settings is limited, and transmission between school staff members is more common than transmission involving students.[9] There is evidence that SARS-CoV-2 transmission is greater in secondary and high schools than elementary schools.[10,11]

As with adults, children and adolescents with underlying conditions such as asthma, chronic lung disease, and cancer are at higher risk than their heathier counterparts for COVID-19-related hospitalization and death. Of the children who have developed severe illness from COVID-19, most have had underlying medical conditions.[12] Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious COVID-19-associated condition that can present with persistent fever, laboratory markers of inflammation and heart damage, and, in severe cases, hypotension and shock.[13] Between May 2020 and March 2021, the CDC received reports of 3,185 cases and 36 deaths that met the definition for MIS-C; most cases occurred in children ages 1 to 14 years (median age 9 years), in males (59%), and in children who were reported as Hispanic or Black (64%).[14]

Other impacts of COVID-19 on adolescents include limited access to basic services such as healthcare and child protective services, and social isolation due to disruption of school, sports, and social group gatherings. Published studies have highlighted increases in symptoms of depression, and anxiety[15,16] and increased rates of suicidal ideation and attempts among adolescents during the pandemic.[17]

2.2 Authorized Vaccines and Therapies for COVID-19

Vaccines to prevent COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks. Pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which allows the FDA to authorize unapproved medical products for use in an emergency when certain criteria are met, the FDA has issued EUAs for three COVID-19 vaccines (Table 1) for use in adults (and for the Pfizer-BioNTech COVID-19 vaccine, use in adolescents ages 16-17 years). The two mRNA vaccines authorized in December 2020 (Pfizer and Moderna) were shown to be >90% effective in preventing COVID-19 in adults, including prevention of severe COVID-19.[18,19] However, no vaccine against COVID-19 has been authorized for use in children and adolescents under 16 years of age.

Table 1. COVID-19 Vaccines Authorized for Emergency Use by the FDA

Sponsor	Regimen	Indicated Population	Date of EUA
Pfizer	2 doses 3 weeks apart	Individuals ≥16 years of age	December 11, 2020
Moderna	2 doses 4 weeks apart	Adults ≥18 years of age	December 18, 2020
Janssen	Single dose	Adults ≥18 years of age	February 27, 2021

No vaccine or other medical product is FDA approved for prevention of COVID-19. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. FDA subsequently issued EUAs for two monoclonal antibody combinations (casirivimab plus imdevimab and bamlanivimab plus etesevimab) for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to severe COVID-19 and/or hospitalization.[20,21]

2.3 EUA Amendment Request for the Pfizer-BioNTech COVID-19 Vaccine

Pfizer, in partnership with BioNTech SE, has developed a vaccine to prevent COVID-19 which is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles. The Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) is administered as a series of two 30-µg intramuscular injections spaced 21 days apart. The vaccine is supplied as a multi-dose vial containing a frozen suspension (-80°C to -60°C) of BNT162b2 that must be thawed and diluted with 1.8 mL of sterile 0.9% sodium chloride, allowing for six 0.3 mL doses. The vaccine is preservative free.

Based on the totality of scientific evidence available at the time, the FDA issued an EUA on December 11, 2020 for use of BNT162b2 to prevent COVID-19 in individuals 16 years of age and older.[1] In the planned final primary efficacy analysis of results from a Phase 2/3 randomized and placebo-controlled trial using BNT162b2 in approximately 44,000 participants, vaccine efficacy after 7 days post Dose 2 was 95% (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the larger group of participants with or without prior infection. Efficacy outcomes were consistently high (≥93%) across demographic subgroups. Secondary and post hoc efficacy analyses also suggested efficacy against severe COVID-19, efficacy against COVID-19 in the time period between Dose 1 and Dose 2, and against COVID-19 in subjects with evidence of SARS-CoV-2 infection prior to vaccination. Assessment of the known and potential benefits of the vaccine outweighed the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. Identified risks included common local and systemic adverse reactions (notably injection site reactions, headache, fever, chills, myalgia, and fatigue, all of which are usually mild to moderate and lasting a few days, with higher frequency in younger vaccine recipients compared with older vaccine recipients) and less commonly lymphadenopathy and allergic reactions.

As of the date of this review, more than 134 million doses of Pfizer-BioNTech COVID-19 Vaccine have been administered in the U.S. Post-authorization surveillance has identified a risk of anaphylaxis, occurring at a rate of 0.46 cases per million doses administered (similar to reported rates of anaphylaxis following licensed preventive vaccines) and occurring primarily in individuals with history of prior severe allergic reactions to other medications or foods. No other safety signals in Pfizer-BioNTech COVID-19 Vaccine recipients 16 years of age and older, including pregnant individuals, have arisen through ongoing active and passive surveillance (see Section 3.3 for additional details). Reported breakthrough cases of COVID-19 among vaccine recipients have been uncommon and have not raised a concern about vaccine-enhanced disease.[22]

On April 9, 2021, Pfizer and BioNTech submitted a request to amend this EUA for the purpose of expanding the use of BNT162b2 to individuals 12 years of age and older. The request is accompanied by clinical trial data evaluating the safety and effectiveness of the vaccine in 2,260 participants 12-15 years of age, which includes a total of 1,131 vaccine recipients, 58.3% of whom had ≥2 months of follow-up after Dose 2. In this age group, vaccine effectiveness was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers at 1 month after Dose 2 in adolescents 12-15 years of age with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE had been demonstrated). Efficacy against COVID-19 disease was also assessed with descriptive analyses in study participants 12-15 years of age.

2.4 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).[23]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in preventing, diagnosing, or treating such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one Phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner. These same requirements apply for this EUA amendment focusing specifically on use in adolescents 12-15 years of age.

2.5 Applicable Guidance for Industry and Regulatory Considerations

An EUA allowing for rapid and widespread deployment of the vaccine to millions of individuals, including healthy people, would need to be supported by clear and compelling evidence of effectiveness and adequate safety follow-up to make a determination of favorable benefit/risk (see guidance for industry "Emergency Use Authorization for Vaccines to Prevent COVID-19" February 2021, originally issued October 2020).[24] These expectations would apply to age-group specific data to support an EUA amendment for use of an unapproved COVID-19 vaccine in adolescents 12-15 years of age. The timing, design, and appropriate endpoints for pediatric studies would be discussed in the context of specific vaccine development programs as described in the guidance for industry "Development and Licensure of Vaccines to Prevent" COVID-19 from June 2020.[25]

Information Needed to Support an EUA Amendment for Use in Adolescents

Effectiveness

Regulatory precedent with other preventive vaccines provides a basis for inference of vaccine effectiveness in pediatric populations based on immunobridging to an adult population in which clinical disease endpoint vaccine efficacy has been demonstrated for the same vaccine (including same dose and regimen). The immune marker(s) used for immunobridging do not need to be scientifically established to predict protection but should be clinically relevant to the

disease. Based on available data in humans and animal models, FDA considers neutralizing antibody titers (a functional measure of the vaccine immune response against SARS-CoV-2) to be clinically relevant for immunobridging to infer effectiveness of COVID-19 vaccines in pediatric age groups. Because no specific neutralizing antibody titer has been established to predict protection against COVID-19, two immunogenicity endpoints (geometric mean titer and seroresponse rate) are considered appropriate for comparing the range of neutralizing antibody responses elicited by the vaccine in adolescent vs. adult populations.

Safety

Considering the burden of COVID-19 in the adolescent age group, and the highly favorable benefit/risk balance for the Pfizer vaccine in adults, FDA determined in discussions with Pfizer that a median safety follow-up of at least 2 months among an overall adolescent study population of at least 1,000 vaccine recipients 12-15 years of age, together with longer-term safety data from younger adult study participants, would be sufficient to assess risks in support of an EUA amendment to allow for use of the vaccine in this age group.

3. FDA Review of Clinical Safety and Effectiveness Data

3.1 Overview of Clinical Studies

The EUA amendment request included data from one ongoing clinical study, summarized in Table 2 below. Study C4591001 is a multi-center, multi-national Phase 1/2/3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study. Data from this study were used to support the existing EUA for individuals 16 years of age and older.[1] The focus of this EUA review is the data for participants 12-15 years of age and a comparison group of participants 16-25 years of age. Additionally, safety data from participants 16-55 years of age (13,069 BNT162b2 recipients, 13,095 placebo recipients) with longer safety follow-up and available data from post-authorization safety surveillance were reviewed to assess for any safety concerns not identified during review of the original EUA request.

Table 2: Study C4591001 in Participants 12 Through 15 and 16 Through 25 Years of Age

Study Number/ Countries	Description	BNT162b2 (30 µg) N	Placebo (Saline) N	Study Status
C4591001 USA, Argentina, Brazil, Germany, South Africa, Turkey	Phase 1/2/3, randomized, placebo-controlled, observer-blind; to evaluate safety, immunogenicity and efficacy of COVID-19 vaccine	Total: 3009 12-15 years: 1134 16-25 years: 1875	Total: 3043 12-15 years: 1130 16-25 years: 1913	Ongoing

N=Number of randomized participants as of March 13, 2021.
Study C4591001 began in April 2020 (first participant, first visit); participants 12-15 years of age: first participant, first visit was October 15, 2020 (implemented according to protocol amendment 7).

3.2 Study C4591001

3.2.1 Design

Study C4591001 is an ongoing, randomized, placebo-controlled, Phase 1/2/3 study being conducted in the U.S., Argentina, Brazil, Germany, South Africa and Turkey. Participants were randomized 1:1 to receive 2 doses of either BNT162b2 or placebo, 21 days apart. Adolescents were added to the protocol during Phase 3, following a review of safety data in young adult

participants. This resulted in three age strata as follows: 12-15 years, 16-55 years, and >55 years and older.

The protocol-specified evaluation for vaccine effectiveness in participants 12-15 years of age was defined as an immunobridging evaluation comparing SARS-CoV-2 50% neutralizing antibody titers at 1 month after Dose 2 with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE has been demonstrated).

Immunogenicity endpoint for adolescents 12 through 15 years of age

- GMR: the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the two age groups (12-15 years and 16-25 years) 1 month after completion of vaccination, in participants without serological or virological evidence of past SARS CoV-2 infection before and during vaccination regimen.
- Immunobridging would be demonstrated upon rejection of the null hypothesis: GMR of neutralizing antibody titers (adolescents to young adults) <0.67-fold, i.e., the lower bound of the 95% CI for the GMR is >0.67.
- Immunobridging data also included a descriptive analysis of the difference in seroresponse rates (adolescents minus young adults) among participants without prior evidence of SARS-CoV-2 infection. Seroresponse was defined as a ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month after Dose 2.

Supplementary to the immunobridging analysis, adolescents were followed for potential cases of COVID-19 to assess VE using the same methods as for participants 16 years of age and older. The primary efficacy endpoint of Study C4591001 was efficacy of the vaccine against laboratory-confirmed COVID-19 in participants without prior SARS-CoV-2 infection. A second primary efficacy endpoint included participants with and without prior SARS CoV-2 infection. COVID case definitions may be found in the review of the EUA for individuals 16 years of age and older.[1] Efficacy against COVID-19 disease was assessed with descriptive analyses in study participants 12-15 years of age.

Per protocol, since December 14, 2020, study participants 16 years of age and older have been progressively unblinded to their treatment assignment (when eligible per local recommendations) and offered BNT162b2 vaccination if they were randomized to placebo. Participants 12-15 years of age were all enrolled at sites in the U.S. and remain blinded to treatment assignment, except for 23 (2%) participants who received placebo (N=1129) and elected to be unblinded when they turned 16 years of age so they could receive the vaccine under the EUA as allowed for individuals 16 years and older.

Evaluation of safety

All participants 12-15 years of age recorded local reactions, systemic events, and antipyretic/pain medication use from Day 1 through Day 7 after each dose in an e-diary. Reactogenicity assessments included solicited injection site reactions (pain, redness, swelling) and systemic AEs (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain). Other safety assessments included: AEs occurring within 30 minutes after each dose, non-serious unsolicited AEs from Dose 1 through 1 month after the last dose, and serious AEs (SAEs) from Dose 1 to the data cut-off or participant's unblinding date (whichever was earlier), all which were recorded on the case report form. The data cut-off date for this EUA amendment was March 13, 2021.

Potential COVID-19 illnesses and their sequelae were not reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. These illnesses were evaluated and reported as SAEs.

Analysis populations

Population	Description
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 2 doses of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	1. All randomized participants who receive at least 1 dose of vaccine. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.
Reactogenicity subset	All 12-15-year-old participants in the safety population plus the subset of the 16-25-year-old participants in the safety population who had e-diary data reported after vaccination.

Phase 3 clinical endpoints and analyses outlined in this review are provided for the following age groups:

- Adolescents 12-15 years of age: immunobridging, efficacy and safety
- Young adults 16-25 years of age: reference group for immunogenicity, solicited local reactions and systemic AEs, unsolicited AEs (within 30 minutes, non-serious through 30 days after each vaccination), and SAEs through 30 days after each vaccination
- Adults 16-55 years of age: supportive safety data (SAEs and adverse events of special interest (AESIs) from larger group of adult participants with longer-term follow-up.

3.2.2 FDA Assessment of Phase 2/3 Follow-Up Duration for Participants 12 Through 15 Years of Age

Participants 12-15 years of age began enrollment into Phase 3 of Study C4591001 on October 15, 2020 (implemented with protocol amendment 7). As of the March 13, 2021 data cutoff for this EUA amendment, a total of 2,260 adolescents (1,131 in the BNT162b2 group and 1,129 in the placebo group) were enrolled and contributed to the safety population; 57.9% of participants had ≥2 months of follow-up after Dose 2 (Table 3).

Table 3. Follow-up Duration After Dose 2, Participants 12 Through 15 Years of Age, Safety Population

	Vaccine Group (as Administered)		
Length of Follow-up[c]	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
<1 Month	13 (1.1)	25 (2.2)	38 (1.7)
≥1 Month to <2 months	458 (40.5)	456 (40.4)	914 (40.4)
≥2 Months to <3 months	612 (54.1)	599 (53.1)	1211 (53.6)
≥3 Months	48 (4.2)	49 (4.3)	97 (4.3)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 3, page 20.
[a] N=number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n=number of subjects with the specified characteristic.
[c] Length of follow-up is the total exposure from Dose 2 to cutoff date or the date of unblinding, whichever date was earlier.

Safety comparator group: As of March 13, 2021, a total of 3,770 participants 16-25 years of age (1,867 in the BNT162b2 group and 1,903 in the placebo group) were enrolled and contributed to the safety population, of which 3,622 (96.1%) and 3,292 (87.3%) participants had ≥1 months and ≥2 month of follow-up, respectively, after Dose 2.

3.2.3 Participant Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 4 (immunogenicity populations), Table 5 (efficacy populations) and Table 6 (safety population). Within each age group, the percentages of participants who discontinued or were lost to follow-up were generally balanced.

For immunogenicity analyses, the Sponsor planned to select a random sample of 280 participants in the BNT162b2 group for each of the two age groups as an immunogenicity subset for immunobridging. Randomization of participants to the immunogenicity subset was conducted through the use of an interactive response technology based on an interactive web-based response to minimize bias. To maintain blinding of the laboratory personnel, 50 participants who had received placebo were randomly selected from each of the two age groups for serology testing. The population for the analysis of the immunogenicity endpoint (Dose 2 evaluable immunogenicity population) included 245 participants 12-15 years of age (209 in the Pfizer BioNTech COVID-19 Vaccine group and 36 in the placebo group) and 218 participants 16-25 years of age (186 in the Pfizer BioNTech COVID-19 Vaccine group and 32 in the placebo group). The majority of exclusions to the immunogenicity analysis population were due to participants not having at least 1 valid and determinate immunogenicity result after Dose 2 (mostly as the result of limited supply of the qualified viral lot at the testing laboratory) and were generally balanced across age and vaccine groups.

Table 4. Disposition of Participants 12 Through 15 Years of Age and 16 Through 25 Years of Age, Immunogenicity Populations

Disposition	12-15 Years BNT162b2 n (%)	16-25 Years BNT162b2 n (%)	12-15 Years Placebo n (%)	16-25 Years Placebo n (%)
Randomized[a]	280 (100.0)	280 (100.0)	50 (100.0)	50 (100.0)
Dose 2 all-available immunogenicity population	210 (75.0)	191 (68.2)	36 (72.0)	34 (68.0)
Participants excluded from Dose 2 all-available immunogenicity population	70 (25.0)	89 (31.8)	14 (28.0)	16 (32.0)

Disposition	12-15 Years BNT162b2 n (%)	16-25 Years BNT162b2 n (%)	12-15 Years Placebo n (%)	16-25 Years Placebo n (%)
Reason for exclusion[b]				
Did not receive 2 vaccinations	1 (0.4)	0	0	0
Did not have at least 1 valid and determinate immunogenicity result after Dose 2	69 (24.6)	89 (31.8)	14 (28.0)	16 (32.0)
Dose 2 evaluable immunogenicity population	209 (74.6)	186 (66.4)	36 (72.0)	32 (64.0)
Participants excluded from evaluable immunogenicity population	71 (25.4)	94 (33.6)	14 (28.0)	18 (36.0)
Reason for exclusion[b]				
Randomized but did not meet all eligibility criteria	0	0	0	0
Did not provide informed consent	0	0	0	0
Did not receive 2 doses of the vaccine to which they were randomly assigned	1 (0.4)	0	0	0
Did not receive Dose 2 within 19-42 days after Dose 1	1 (0.4)	2 (0.7)	0	2 (4.0)
Did not have at least 1 valid and determinate immunogenicity result after Dose 2	69 (24.6)	89 (31.8)	14 (28.0)	16 (32.0)
Did not have blood collection within 28-42 days after Dose 2	3 (1.1)	16 (5.7)	0	3 (6.0)
Had important protocol deviation(s) as determined by the clinician	0	0	0	1 (2.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table B, page 1.
[a] These values are the denominators for the percentage calculations.
[b] Participants may have been excluded for more than 1 reason.
NA=not applicable

Table 5. Disposition of Participants 12 Through 15 Years of Age, Efficacy Populations

Disposition	BNT162b2 n (%)	Placebo n (%)	Total n (%)
Randomized[a]	1134 (100.0)	1130 (100.0)	2264 (100.0)
Dose 1 all-available efficacy population	1131 (99.7)	1129 (99.9)	2260 (99.8)
Participants without evidence of infection before Dose 1	1028 (90.7)	1023 (90.5)	2051 (90.6)
Participants excluded from Dose 1 all-available efficacy population	3 (0.3)	1 (0.1)	4 (0.2)
Reason for exclusion[b]			
Did not receive at least 1 vaccination	3 (0.3)	1 (0.1)	4 (0.2)
Dose 2 all-available efficacy population	1123 (99.0)	1117 (98.8)	2240 (98.9)
Participants without evidence of infection prior to 7 days after Dose 2	1008 (88.9)	983 (87.0)	1991 (87.9)
Participants excluded from Dose 2 all-available efficacy population	11 (1.0)	13 (1.2)	24 (1.1)
Reason for exclusion[b]			
Did not receive 2 vaccinations	10 (0.9)	13 (1.2)	23 (1.0)
Unblinded prior to 7 days after Dose 2	1 (0.1)	0	1 (0.0)
Evaluable efficacy population	1119 (98.7)	1110 (98.2)	2229 (98.5)
Subjects without evidence of infection prior to 7 days after Dose 2	1005 (88.6)	978 (86.5)	1983 (87.6)
Participants excluded from evaluable efficacy (7 days) population	15 (1.3)	20 (1.8)	35 (1.5)

Disposition	BNT162b2 n (%)	Placebo n (%)	Total n (%)
Reason for exclusion[b]			
Randomized but did not meet all eligibility criteria	1 (0.1)	0	1 (0.0)
Did not provide informed consent	0	0	0
Did not receive all vaccinations as randomized or did not receive Dose 2 within the predefined window (19-23 days after Dose 1)	14 (1.2)	19 (1.7)	33 (1.5)
Had other important protocol deviations on or prior to 7 days after Dose 2	0	2 (0.2)	2 (0.1)
Unblinded prior to 7 days after Dose 2	1 (0.1)	0	1 (0.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table C, pages 2-3.
Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
[a] These values are the denominators for the percentage calculations.
[b] Participants may have been excluded for more than 1 reason.

Table 6. Disposition of Participants 12 Through 15 Years of Age and 16 Through 25 Years of Age, Safety Populations

Treatment Group	12-15 Years BNT162b2 n (%)	16-25 Years BNT162b2 n (%)	12-15 Years Placebo n (%)	16-25 Years Placebo n (%)
Randomized (N)[a]	1134 (100.0)	1875 (100.0)	1130 (100.0)	1913 (100.0)
Not vaccinated	3 (0.3)	6 (0.3)	1 (0.1)	7 (0.4)
Vaccinated				
Completed 1 dose	1131 (99.7)	1869 (99.7)	1129 (99.9)	1906 (99.6)
Completed 2 doses	1124 (99.1)	1826 (97.4)	1117 (98.8)	1836 (96.0)
Safety population	1131 (99.7)	1867 (99.5)	1129 (99.9)	1903 (95.9)
Reactogenicity subset	1131 (99.7)	537 (28.6)	1129 (99.9)	561 (29.3)
HIV-positive	0	1 (0.05)	0	0
Participants excluded from safety population	3 (0.26)	8 (0.42)	1 (0.08)	10 (0.52)
Reason for exclusion[b]				
Did not receive study vaccination	3 (0.26)	6 (0.32)	1 (0.08)	7 (0.36)
Unreliable data due to lack of PI oversight	0	2 (0.10)	0	3 (0.15)
Completed at least 2 months follow-up after Dose 2[c]	660 (58.4)	1645 (88.1)	648 (57.4)	1647 (86.5)
Completed 1-month after Dose 2 visit (vaccination period)	1118 (98.6)	1803 (96.2)	1102 (97.5)	1807 (94.5)
Discontinued from vaccination period but continued in the study up to 1-month after Dose 2 visit	7 (0.6)	13 (0.7)	17 (1.5)	42 (2.2)
Discontinued after Dose 1 and before Dose 2	7 (0.6)	12 (0.6)	10 (0.9)	36 (1.9)
Discontinued after Dose 2 and before 1-month post-Dose 2 visit	0	1 (0.1)	7 (0.6)	6 (0.3)
Reason for discontinuation from vaccination period				
No longer meets eligibility criteria	3 (0.3)	4 (0.2)	10 (0.9)	26 (1.4)
Withdrawal by subject	0	6 (0.3)	1 (0.1)	1 (0.1)
Pregnancy	0	1 (0.1)	0	3 (0.2)
Adverse event	2 (0.2)	1 (0.1)	0	0
Physician decision	1 (0.1)	0	0	2 (0.1)
Protocol deviation	0	0	1 (0.1)	2 (0.1)
Lost to follow-up	0	0	0	1 (0.1)

Treatment Group	12-15 Years BNT162b2 n (%)	16-25 Years BNT162b2 n (%)	12-15 Years Placebo n (%)	16-25 Years Placebo n (%)
Other	1 (0.1)	1 (0.1)	5 (0.4)	7 (0.4)
Withdrawn from study before 1-month post-Dose 2 visit	0	45 (2.4)	2 (0.2)	56 (2.9)
Withdrawn after Dose 1 and before Dose 2	0	25 (1.3)	1 (0.1)	34 (1.8)
Withdrawn after Dose 2 and before 1-month post-Dose 2 visit	0	20 (1.1)	1 (0.1)	22 (1.2)
Reason for withdrawal				
Adverse event	0	0	0	1 (0.1)
Death	0	0	0	0
Withdrawal by subject	0	14 (0.7)	0	19 (1.0)
Lost to follow-up	0	29 (1.5)	0	32 (1.7)
Protocol deviation	0	0	1 (0.1)	1 (0.1)
Withdrawal by parent/guardian	0	1 (0.1)	1 (0.1)	0
Physician decision	0	0	0	1 (0.1)
Other	0	1 (0.1)	0	2 (0.1)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table D, pages 3-4.
Note: The Human immunodeficiency virus (HIV)-positive subject included in this summary is not included in the analyses of the overall safety objectives. Safety data based on HIV-positive subjects were analyzed separately.
[a] N: denominator used for the percentage calculations.
[b] Participants may have been excluded for more than 1 reason.
[c] The numbers in this row are based on subjects who got dose 2 as administered. Duration of follow-up is based on blinded placebo-controlled follow-up period only.
PI=principal investigator

3.2.4 Demographics and Other Baseline Characteristics

The Dose 2 evaluable immunogenicity population included 245 participants 12-15 years of age (209 in the Pfizer BioNTech COVID-19 Vaccine group and 36 in the placebo group) and 218 participants 16-25 years of age (186 in the Pfizer BioNTech COVID-19 Vaccine group and 32 in the placebo group) (Table 7).

The Dose 2 evaluable immunogenicity population of 12-15-year-olds who received BNT162b2 included 49.3% females, 88.0% White, 7.7% African American, 2.4% Asian, and <2% from other racial groups; 10.5% of participants were Hispanic/Latino. The median age was 14 years. One or more comorbidities that increase the risk of severe COVID-19 disease were present among 21.5% of participants. Geographically, all participants lived in the U.S. For participants 16-25 years of age in the immunogenicity subset, the demographics characteristics were generally similar to those described in the adolescent population, with the exception of comorbidities and obesity, both of which are slightly more prevalent in the young adult age group.

Table 7. Demographics and Other Baseline Characteristics, Participants 12 Through 15 Years of Age and 16 Through 25 Years of Age, Dose 2 Evaluable Immunogenicity Population[a]

Characteristic	12-15 Years BNT162b2 (N=209) n (%)	16-25 Years BNT162b2 (N=186) n (%)	12-15 Years Placebo (N=36) n (%)	16-25 Years Placebo (N=32) n (%)
Sex: Female	103 (49.3)	94 (50.5)	15 (41.7)	18 (56.3)
Sex: Male	106 (50.7)	92 (49.5)	21 (58.3)	14 (43.8)
Age: Mean years (SD)	13.5 (1.12)	20.6 (3.09)	13.4 (1.17)	20.3 (3.05)
Age: Median (years)	14.0	21.0	13.0	19.5

Characteristic	12-15 Years BNT162b2 (N=209) n (%)	16-25 Years BNT162b2 (N=186) n (%)	12-15 Years Placebo (N=36) n (%)	16-25 Years Placebo (N=32) n (%)
Race: American Indian or Alaska Native	1 (0.5)	3 (1.6)	0	1 (3.1)
Race: Asian	5 (2.4)	10 (5.4)	1 (2.8)	1 (3.1)
Race: Black or African American	16 (7.7)	15 (8.1)	3 (8.3)	2 (6.3)
Race: Native Hawaiian or other Pacific Islander	0	3 (1.6)	0	0
Race: White	184 (88.0)	147 (79.0)	31 (86.1)	28 (87.5)
Race: Multiracial	3 (1.4)	6 (3.2)	1 (2.8)	0
Race: Not reported	0	2 (1.1)	0	0
Ethnicity: Hispanic or Latino	22 (10.5)	31 (16.7)	2 (5.6)	7 (21.9)
Ethnicity: Not Hispanic or Latino	187 (89.5)	154 (82.8)	34 (94.4)	25 (78.1)
Ethnicity: Not reported	0	1 (0.5)	0	0
Obese[b]: Yes	24 (11.5)	43 (23.1)	3 (8.3)	4 (12.5)
Obese: No	185 (88.5)	143 (76.9)	33 (91.7)	28 (87.5)
Comorbidities[c]: Yes	45 (21.5)	56 (30.1)	7 (19.4)	9 (28.1)
Comorbidities: No	164 (78.5)	130 (69.9)	29 (80.6)	23 (71.9)
Baseline evidence of prior SARS-CoV-2 infection: Negative	194 (92.8)	178 (95.7)	33 (91.7)	31 (96.9)
Baseline evidence of prior SARS-CoV-2 infection: Positive	10 (4.8)	8 (4.3)	2 (5.6)	1 (3.1)
Baseline evidence of prior SARS-CoV-2 infection: Unknown	5 (2.4)	0	1 (2.8)	0
Region: North America	209 (100.0)	186 (100.0)	36 (100.0)	32 (100.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table E, page 4-5.
[a] All elig ble randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
[b] Obese is defined as BMI ≥30 kg/m2 (≥16 years of age) or BMI ≥95th percentile (12-15 years of age).
[c] Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis (see Appendix A) or obesity alone.
NA=not applicable

The demographic characteristics of the evaluable efficacy population in participants 12-15 years of age for the VE analyses (N=1005 vaccine group, N=978 placebo group) are similar to the baseline characteristics of the Dose 1 all-available efficacy population.

The Dose 1 all-available efficacy population of 12-15-year-olds (BNT162b2 n=1,131, placebo n=1,129) were the same individuals as the 12-15-year-olds as in the safety population (Table 8).

Safety population: Among participants 12-15 years of age, the median age was 14 years, and all participants lived in the U.S. Among participants 16-25 years of age, the median age was 18 years in the BNT162b2 group and 19 years in the placebo group; 81.2% and 77.4% participants, respectively, lived in the U.S.

Table 8. Demographics and Other Baseline Characteristics, Participants 12 Through 15 Years of Age and 16 Through 25 Years of Age (Reactogenicity Subset), Safety Populations[a]

Characteristic	12-15 Years BNT162b2 (N=1131) n (%)	16-25 Years BNT162b2 (N=537) n (%)	12-15 Years Placebo (N=1129) n (%)	16-25 Years Placebo (N=561) n (%)
Sex: Female	564 (49.9)	282 (52.5)	544 (48.2)	292 (52.0)
Sex: Male	567 (50.1)	255 (47.5)	585 (51.8)	269 (48.0)

Characteristic	12-15 Years BNT162b2 (N=1131) n (%)	16-25 Years BNT162b2 (N=537) n (%)	12-15 Years Placebo (N=1129) n (%)	16-25 Years Placebo (N=561) n (%)
Age: Mean years (SD)	13.6 (1.11)	19.4 (3.26)	13.6 (1.11)	19.6 (3.33)
Age: Median (years)	14.0	18.0	14.0	19.0
Race: American Indian or Alaska Native	4 (0.4)	7 (1.3)	3 (0.3)	1 (0.2)
Race: Asian	72 (6.4)	22 (4.1)	71 (6.3)	21 (3.7)
Race: Black or African American	52(4.6)	47 (8.8)	57 (5.0)	50 (8.9)
Race: Native Hawaiian or other Pacific Islander	3 (0.3)	3 (0.6)	0	1 (0.2)
Race: White	971 (85.9)	445 (82.9)	962 (85.2)	466 (83.1)
Race: Multiracial	23 (2.0)	12 (2.2)	29 (2.6)	19 (3.4)
Race: Not reported	6 (0.5)	1 (0.2)	7 (0.6)	3 (0.5)
Race: Other	0	0	0	0
Ethnicity: Hispanic or Latino	132 (11.7)	112 (20.9)	130 (11.5)	105 (18.7)
Ethnicity: Not Hispanic or Latino	997 (88.2)	423 (78.8)	996 (88.2)	456 (81.3)
Ethnicity: Not reported	2 (0.2)	2 (0.4)	3 (0.3)	0
Obese: Yes	143 (12.6)	80 (14.9))	128 (11.3)	101 (18.0)
Obese: No	988 (87.4)	80 (14.9)	1001 (88.7)	460 (82.0)
Comorbidities[b]: Yes	248 (21.9)	126 (23.5)	240 (21.3)	144 (25.7)
Comorbidities: No	883 (78.1)	411 (76.5)	889 (78.7)	417 (74.3)
Baseline evidence of prior SARS-CoV-2 infection: Negative	1028 (90.9)	497 (92.6)	1023 (90.6)	522 (93.0)
Baseline evidence of prior SARS-CoV-2 infection: Positive	46 (4.1)	522 (93.0)	47 (4.2)	522 (93.0)
Baseline evidence of prior SARS-CoV-2 infection: Missing	57 (5.0)	10 (1.9)	59 (5.2)	5 (0.9)
Region: North America	1131 (100.0)	436 (81.2)	1129 (100.0)	434 (77.4)
Country: Argentina	0	20 (3.7)	0	28 (5.0)
Country: Brazil	0	24 (4.5)	0	19 (3.4)
Country: Germany	0	11 (2.0)	0	20 (3.6)
Country: South Africa	0	34 (6.3)	0	45 (8.0)
Country: Turkey	0	12 (2.2)	0	15 (2.7)

Sources: EUA 27034.132, eua-amend-12-15-years.pdf, Table 5, page 23 and c4591001--12-15-tables-figures.docx, Table P, page 7-9.
[a] All randomized participants who receive at least 1 dose of the study intervention.
[b] Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis (see Appendix A) or obesity alone (BMI ≥30 kg/m2 [≥16 years of age] or BMI ≥95th percentile [12-15 years of age].[b] Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis (see Appendix A) or obesity alone.(BMI ≥30 kg/m2 [≥16 years of age] or BMI ≥95th percentile [12-15 years of age].

3.2.5 Vaccine Effectiveness

Immunogenicity

The immune response to BNT162b2 in adolescents 12-15 years of age was noninferior to that observed in young adults 16-25 years of age, based on SARS-CoV-2 50% neutralizing titers at 1 month after Dose 2 in participants without prior evidence of SARS-CoV-2 infection. The geometric mean titer (GMT) ratio of adolescent to young adult neutralizing antibody titers was

1.76 (2-sided 95% CI: 1.47, 2.10), meeting the 1.5-fold non-inferiority criterion (i.e., lower bound of the 2-sided 95% CI for GMR >0.67).

Table 9. Geometric Mean SARS-CoV-2 Neutralizing Titers (NT50) 1 Month After BNT162b2 Dose 2 in Participants 12 Through 15 and 16 Through 25 Years of Age, Participants Without Evidence of Infection up to 1 Month After Dose 2, Dose 2 Evaluable Immunogenicity Population

Study Group	12-15 Years N=190 GMT (95% CI)	16-25 Years N=170 GMT (95% CI)	GMT Ratio [12-15 Years/ 16-25 Years] (95% CI)	Met Predefined Success Criterion[a]
BNT162b2	1239.5 (1095.5, 1402.5)	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Yes

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 23, page 85.
[a] Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.
N=Number of participants with valid and determinate assay results for the specified assay at 1 month after Dose 2.
GMT=geometric mean titer

The GMR of SARS CoV-2 neutralizing titers one month after Dose 2 did not vary by demographic subgroup, although some subgroups were too small to evaluate by protocol-specified methods.

Table 10. Subgroup Analyses of Geometric Mean SARS-CoV-2 Neutralizing Titers (NT 50) One Month After BNT162b2 Dose 2 in Participants 12 Through 15 Years of Age and 16 Through 25 Years of Age, Dose 2 All-Available Immunogenicity Population

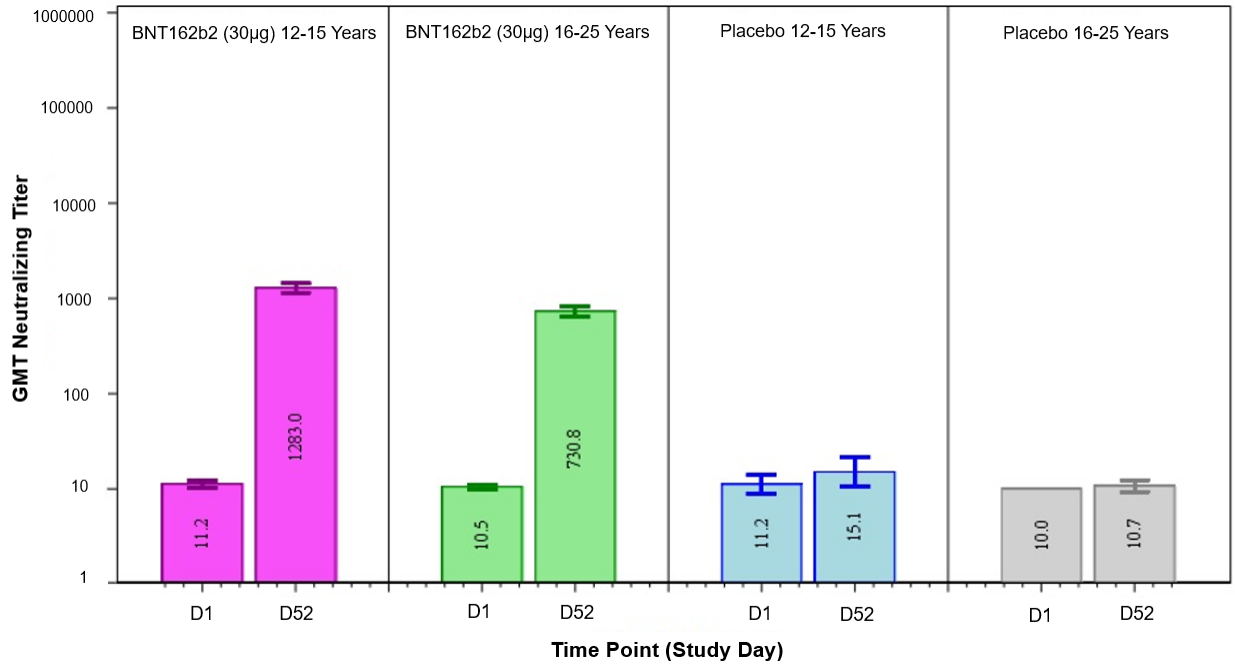
Subgroup	12-15 Years N, GMT (95% CI)	16-25 Years N, GMT (95% CI)	GMT Ratio [definition] (95% CI)
Comorbid condition[a]: Yes	45, 1460.3 (1218.2, 1750.5)	56, 712.4 (546.0,929.5)	2.05 (1.49, 2.82)
Comorbid condition: No	163, 1239.7 (1075.2, 1429.3)	134, 732.1 (641.6, 835.5)	1.69 (1.40, 2.05)
Obese: Yes	24, 1596.9 (1233.2, 2067.8)	43, 802.4 (613.5, 1049.4)	1.99 (1.33, 2.97)
Obese: No	184, 1284.4 (1097.1, 1420.5)	147, 705.4 (615.9, 807.9)	1.77 (1.47, 2.14)
Baseline SARS-CoV-2: Positive	10, 2342.2 (1308.7, 4191.8)	8, 1439.2 (727.1, 2848.7)	1.63 (0.72, 3.69)
Baseline SARS-CoV-2: Negative	193, 1240.9 (1098.7, 1401.5)	182, 704.7 (624.1, 795.9)	1.76 (1.48, 2.09)
Baseline SARS-CoV-2: Unknown	5, 1458.7 (479.2, 4440.9)	0, NE (NE, NE)	NE
Sex: Female	102, 1315.5 (1123.4, 1540.3)	98, 793.4 (665.9, 945.2)	1.66 (1.31, 2.09)
Sex: Male	106, 1255.2 (1051.3, 1498.5)	92, 661.0 (560.2, 780.0)	1.90 (1.49, 2.42)
Ethnicity: Hispanic or Latino	22, 1276.2 (917.9, 1774.4)	31, 662.4 (472.3, 928.9)	1.93 (1.20, 3.11)
Ethnicity: Not Hispanic or Latino	186, 1285.4 (1132.0, 1459.4)	158, 743.4 (652.9, 846.4)	1.73 (1.44, 2.07)
Ethnicity: Not reported	0, NE (NE, NE)	1,318.0 (NE, NE)	NE
Race: American Indian or Alaska Native	1, 908.0 (NE, NE)	3, 1130.7 (13.7, 93052.6)	0.80 (NE, NE)
Race: Asian	5, 1338.9 (625.6, 2865.8)	10, 649.6 (408.5, 1033.1)	2.06 (0.97, 4.38)

Subgroup	12-15 Years N, GMT (95% CI)	16-25 Years N, GMT (95% CI)	GMT Ratio [definition] (95% CI)
Race: Black or African American	16, 1377.3 (963.1, 1969.4)	15, 803.4 (409.7, 1575.8)	1.71 (0.82, 3.59)
Race: Native Hawaiian or Other Pacific Islander	0, NE (NE, NE)	4, 756.5 (184.9, 3094.1)	NE
Race: White	183, 1286.2 (1129.4, 1464.9)	150, 720.4 (633.2, 819.7)	1.79 (1.48, 2.15)
Race: Multiracial	3, 848.4 (224.8, 3202.1)	6, 741.5 (304.5, 1805.7)	1.14 (0.31, 4.16)
Race: Not reported	0, NE (NE, NE)	2, 486.7 (2.2, 108697.3)	NE

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Table H, pages 6-8.
[a] Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis (see Appendix A) or obesity alone (BMI ≥30 kg/m2 [≥16 years of age] or BMI ≥95th percentile [12-15 years of age]).
N=Number of subjects with valid and determinate assay results for the specified assay at 1 month after Dose 2.
GMT=geometric mean titer, NE=not estimable

The baseline SARS-CoV-2 neutralizing antibody GMTs obtained prior to vaccination were equally low in both of the age groups, with an observed increase in GMTs one month after Dose 2 in vaccine participants (Figure 1).

Figure 1. Geometric Mean Titers: SARS-CoV-2 Neutralization Assay – NT50 – Participants 12 Through 15 and 16 Through 25 Years of Age, Dose 2 Evaluable Immunogenicity Population



Source: EUA 27034, amendment 132, Figure 5; eua-amend-12-15-years.pdf, page 89.
D=day, GMT=geometric mean titer, NT50=50% neutralizing titer
Note: Number within each bar denotes geometric mean titer.

Seroresponse rates among participants without prior evidence of SARS-CoV-2 infection are displayed in Table 11, below. A ≥4-fold rise in SARS-CoV-2 50% neutralizing titers from before vaccination to 1 month after Dose 2 was seen in 97.9% of adolescents and 100% of young adults (difference in seroconversion rates: -2.1%; 95% CI: -6.0%, 0.9%). Of the 3 adolescents

for whom laboratory results did not meet the seroresponse definition, 2 of them failed to respond, with negative neutralizing antibody titers before and after vaccination. The other adolescent had a baseline positive neutralizing antibody titer of 776 despite having a baseline negative N-binding antibody titer and had a titer of 962 at 1 month after Dose 2, which was not an increase of at least 4-fold as required to meet the seroresponse definition.

Table 11. Seroconversion Rates – NT50 – 1 Month After BNT162b2 Dose 2, Participants 12 Through 15 and 16 Through 25 Years of Age, Participants Without Evidence of Infection up to 1 Month After Dose 2, Dose 2 Evaluable Immunogenicity Population

Study Group	12-15 Years N=143 n, SCR (%) (95% CI)	16-25 Years N=124 n, SCR (%) (95% CI)	Difference in Seroconversion Rates[a] (95% CI)
BNT162b2	140 (97.9) (94.0, 99.6)	124 (100.0) (97.1, 100.0)	-2.1 (-6.0, 0.9)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 23, page 86.
[a] Seroconversion is defined as achieving a ≥4-fold rise from baseline (before vaccination).
N=number of participants with valid and determinate assay results for the specified assay both before vaccination and at 1 month after Dose 2.
n=number of participants with ≥4-fold rise from before vaccination to 1 month after Dose 2
SCR=seroconversion rate

Clinical disease endpoint efficacy

The protocol-specified final analysis of efficacy was completed with a data cutoff date of November 14, 2020. At that time, only 100 participants 12-15 years of age (49 in the BNT162b2 group and 51 in the placebo group) had enrolled in the study, and there were no confirmed COVID-19 cases in this age group. Therefore, additional descriptive analyses of VE in adolescents 12-15 years of age were conducted with all cases accrued during blinded follow-up to a data cutoff date of March 13, 2021.

For the first efficacy endpoint in participants 12-15 years of age without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, the observed VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 100.0%. The case split was 0 COVID-19 cases in the BNT162b2 group compared to 16 COVID-19 cases in the placebo group (Table 12). The 95% confidence interval for the VE was 75.3% to 100.0%.

Table 12. Vaccine Efficacy, Participants 12 Through 15 Years of Age Without Evidence of Infection Prior to 7 Days After Dose 2, Evaluable Efficacy Population

Endpoint	BNT162b2 N[a]=1005 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=978 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence from 7 days after Dose 2 in subjects without evidence of prior SARS-CoV-2 infection	0, 0.154 (1001)	16, 0.147 (972)	100.0 (75.3, 100.0)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 18, page 76.
[a] N=Number of participants in the specified group.
[b] n1=Number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
[d] n2=Number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE based on the Clopper-Pearson method adjusted to the surveillance time.

For the second efficacy endpoint in participants 12-15 years of age with and without evidence of SARS-CoV-2 infection before and during vaccination regimen, the observed VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was also 100.0%, with 0 and 18 cases in the BNT162b2 and placebo groups, respectively. The 95% confidence interval for the VE was 78.1% to 100.0%.

Subgroup analyses of vaccine efficacy

The demographics of the participants with confirmed COVID-19 cases contributing to the efficacy analysis are displayed below in Table 13. All confirmed COVID-19 cases occurred in the placebo group in participants who had negative baseline SARS-CoV-2 prior infection status and who identified as White.

Table 13. Demographic Characteristics, Participants 12 Through 15 Years of Age With Protocol-Defined COVID-19 (With or Without Evidence of Infection Prior to 7 Days After Dose 2)

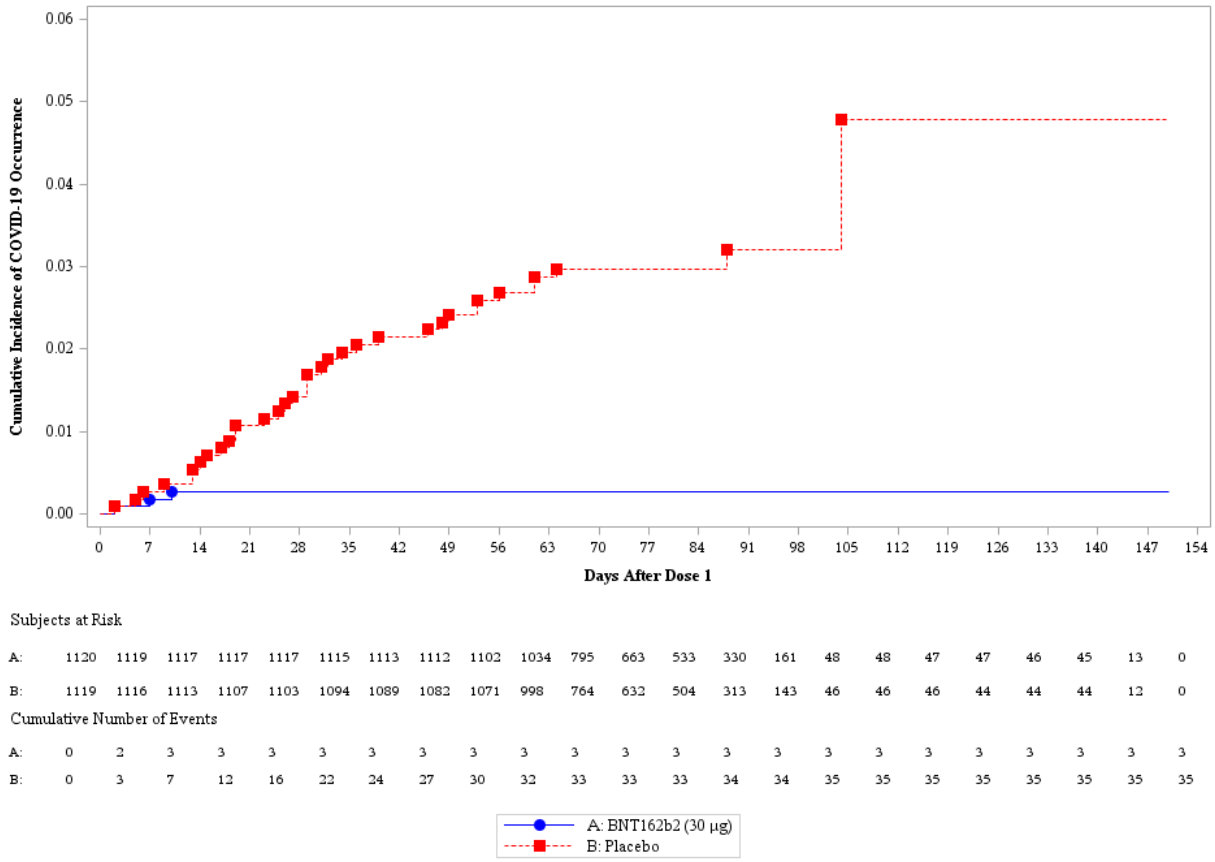
Characteristic	BNT162b2 N=0 n (%)	Placebo N=18 n (%)
Sex: Female	0	6 (33.3)
Sex: Male	0	12 (66.7)
Age at vaccination: Mean years (SD)	0	13.9 (1.16)
Age at vaccination: Median (years)	0	14.0
Race: American Indian or Alaska Native	0	0
Race: Asian	0	0
Race: Black or African American	0	0
Race: Native Hawaiian or Other Pacific Islander	0	0
Race: White	0	18 (100.0)
Race: Multiracial	0	0
Ethnicity: Hispanic or Latino	0	5 (27.8)
Ethnicity: Not Hispanic or Latino	0	13 (72.2)
Comorbidities[a]: Yes	0	7 (38.9)
Comorbidities: No	0	11 (61.1)
Comorbidity: Obesity	0	4 (22.2)
Baseline SARS-CoV-2 Status: Negative	0	18 (100.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables L and M1, pages 12-14.
[a] Comorbidities that increase the risk of severe COVID-19 disease, defined as at least one Charlson index diagnosis (see Appendix A) or obesity alone (BMI ≥30 kg/m^2 [≥16 years of age] or BMI ≥95th percentile [12-15 years of age]).

Cumulative incidence curves

Based on the cumulative incidence curve for the all-available efficacy population after Dose 1 (Figure 2), there are similar numbers of COVID-19 cases in the BNT162b2 and placebo groups until approximately 14 days after Dose 1, at which time point, the curves diverge, with more cases accumulating in the placebo group than in the BNT162b2 group. During the follow-up time of approximately 2 months following the second dose, there does not appear to be waning protection in the BNT162b2 group.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Participants 12 Through 15 Years of Age, Dose 1 All-Available Efficacy Population



Source: EUA 27034, amendment 132; c4591001-508-compliant-tables-12-15.pdf, page 15.

Severe COVID-19 cases

There were no reports of severe COVID-19 cases (and no cases of MIS-C) in participants 12-15 years of age.

Additional efficacy analyses

Additional analyses of the efficacy endpoint were conducted to evaluate the all-available efficacy population of participants 12-15 years of age, regardless of evidence of prior infection from Dose 1 through 7 days after Dose 2 (Table 14).

Table 14. Primary Efficacy Endpoint, Participants 12 Through 15 Years of Age, Dose 1 All-Available Efficacy Population

Efficacy Endpoint	BNT162b2 N[a]=1131 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=1129 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)[e]
First COVID-19 occurrence after Dose 1	3 0.257 (1120)	35 0.250 (1119)	91.6 (73.5, 98.4)
After Dose 1 to before Dose 2	3	12	75.0 (7.4, 95.5)
Dose 2 to 7 days after Dose 2	0	5	100.0 (-9.1, 100.0)
≥7 Days after Dose 2	0	18	100.0 (77.3, 100.0)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables N, pages 16.
[a] N=number of participants in the specified group.
[b] n1=number of participants meeting the endpoint definition.
[c] Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
[d] n2=number of participants at risk for the endpoint.
[e] Confidence interval (CI) for VE is derived based on the Clopper-Pearson method (adjusted for surveillance time for overall row).

VE in participants in the all-available efficacy population was similar to results in the evaluable efficacy population. The VE for the prevention of COVID-19 disease after Dose 1 is 91.6%, in the all-available efficacy population. Based on the number of cases accumulated after Dose 1 and before Dose 2, there does seem to be some protection against COVID-19 disease following one dose; however, the point estimate is lower than efficacy post-Dose 2, and post-Dose 1 data do not provide information about longer term protection beyond 21 days after a single dose.

3.2.6 Safety

Overview of adverse events

Table 15 summarizes adverse events in the safety population. All participants 12-15 years of age in the safety population were also enrolled in the reactogenicity subset. Of 3,788 participants 16-25 years of age, 29% were included in the reactogenicity subset.

Table 15. Safety Overview, Participants 12 Through 15 Years and Participants 16 Through 25 Years of Age

Event	12-15 Years BNT162b2 n/N (%)	12-15 Years Placebo n/N (%)	16-25 Years BNT162b2 n/N (%)
Immediate unsolicited AE within 30 minutes after vaccination[a]			
Dose 1	0/1131 (0.0)	4/1129 (0.4)	11/1866 (0.6)
Dose 2	2/1124 (0.2)	3/1117 (0.3)	7/1818 (0.4)
Solicited injection site reaction within 7 days[a]			
Dose 1	976/1127 (86.6)	271/1127 (24.0)	445/531 (83.8)
Dose 2	872/1097 (79.5)	198/1078 (18.4)	381/488 (78.1)
Solicited systemic AE within 7 days[a]			
Dose 1	877/1127 (77.8)	636/1127 (56.4)	403/531 (75.9)
Dose 2	904/1097 (82.4)	439/1078 (40.7)	396/488 (81.1)
From Dose 1 through 1 month after Dose 2[b]			
Unsolicited non-serious AE	64/1131 (5.7)	66/1129 (5.8)	521/1866 (27.9)
SAE	4/1131 (0.4)	1/1129 (0.1)	6/1866 (0.3)

Event	12-15 Years BNT162b2 n/N (%)	12-15 Years Placebo n/N (%)	16-25 Years BNT162b2 n/N (%)
From Dose 1 to cutoff date or participant blinding (whichever is earlier)[b]			
SAE	5/1131 (0.4)	2/1129 (0.2)	8/1866 (0.4)
Withdrawal due to AEs	2/1131(0.2)	0	2/1866 (0.1)
Deaths	0	0	0

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables Q and Q.1, pages 17-18.
n: number of participants reporting the adverse event.
[a] N: number of participants in the specified age group in the reactogenicity subset of the safety population with data available for the adverse event.
[b] N: number of participants in the specified age group in the safety population.

Immediate AEs

12-15-year-olds
After Dose 1:

- No BNT162b2 recipients reported an immediate AE
- Four (0.4%) placebo recipients reported a total of 5 AEs: injection site pain [n=3], headache [n=1], dizziness [n=1]

After Dose 2:

- Two (0.2%) BNT162b2 recipients reported a total of 2 AEs: injection site pain [n=1], dizziness [n=1]
- Three (0.3%) placebo recipients reported a total of 4 AEs: injection site pain [n=1], fatigue [n=1], chills [n=1], rash [n=1]

The immediate AEs described above were consistent with solicited reactions/events reported among participants in the reactogenicity subset during the first 7 days following vaccination.

One (1) BNT162b2 recipient and 1 placebo recipient reported symptoms on the day of vaccination that were consistent with pre-syncope (after BNT162b2 Dose 2 and after placebo dose 1, respectively). Vasovagal reactions are not uncommon in adolescents following vaccinations and other medical procedures involving needlesticks; the Prescribing Information and Fact Sheet for Healthcare Providers for the authorized Pfizer-BioNTech COVID-19 Vaccine include a warning about measures to avoid injury following vasovagal/syncopal episodes in the immediate post-vaccination period.

Comparator group of 16-25-year-olds: Among the BNT162b2 and placebo groups, the immediate AEs after Dose 1 and after Dose 2 were 0.4%-0.6%, and mostly due to injection site pain.

Anaphylaxis: There were no reports of anaphylaxis in the 12-15-year or 16-25-year age groups through the cutoff date of March 13, 2021.

Solicited local reactions and systemic adverse events

Solicited local reactions

For BNT162b2 recipients in both age groups, injection site pain was the most frequent solicited local adverse reaction. The median onset for all solicited local reactions after either BNT162b2 dose was Day 1 (day of vaccination) to Day 3, and the median duration was 1-3 days. Local

reactions occurred more frequently after Dose 1 than after Dose 2. Injection site reactions following both doses were mostly mild to moderate, and frequencies of severe local reactions were lower in participants 12-15 years of age than in participants 16-25 years of age.

Among 12-15-year-olds, injection site reactions were more frequent in the BNT162b2 group than in the placebo group.

Table 16. Frequency of Solicited Local Reactions Within 7 Days After Each Dose, by Maximum Severity, Participants 12 Through 15 Years of Age and Participants 16 Through 25 Years of Age, Reactogenicity Subset[a]

Event	12-15 Years BNT162b2 Dose 1 N=1127 n (%)	12-15 Years Placebo Dose 1 N=1127 n (%)	12-15 Years BNT162b2 Dose 2 N=1097 n (%)	12-15 Years Placebo Dose 2 N=1078 n (%)	16-25 Years BNT162b2 Dose 1 N=531 n (%)	16-25 Years BNT162b2 Dose 2 N=488 n (%)
Pain at the injection site[b]						
Any[d]	971 (86.2)	263 (23.3)	866 (78.9)	193 (17.9)	443 (83.4)	378 (77.5)
Mild	467 (41.4)	227 (20.1)	466 (42.5)	164 (15.2)	204 (38.4)	202 (41.4)
Moderate	493 (43.7)	36 (3.2)	393 (35.8)	29 (2.7)	227 (42.7)	169 (34.6)
Severe	11 (1.0)	0	7 (0.6)	0	12 (2.3)	7 (1.4)
Redness[c]						
Any[d]	65 (5.8)	12 (1.1)	55 (5.0)	10 (0.9)	34 (6.4)	28 (5.7)
Mild	44 (3.9)	11 (1.0)	29 (2.6)	8 (0.7)	25 (4.7)	18 (3.7)
Moderate	20 (1.8)	1 (0.1)	26 (2.4)	2 (0.2)	7 (1.3)	9 (1.8)
Severe	1 (0.1)	0	0	0	2 (0.4)	1 (0.2)
Swelling[c]						
Any[d]	78 (6.9)	11 (1.0)	54 (4.9)	6 (0.6)	44 (8.3)	33 (6.8)
Mild	55 (4.9)	9 (0.8)	36 (3.3)	4 (0.4)	31 (5.8)	23 (4.7)
Moderate	23 (2.0)	2 (0.2)	18 (1.6)	2 (0.2)	12 (2.3)	10 (2.0)
Severe	0	0	0	0	1 (0.2)	0

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables R and R.1, pages 18-19.
%:n/N. n=number of participants in the specified age group with the specified reaction. N=number of reactogenicity subset participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] All randomized participants in the reactogenicity subset who received at least 1 dose of the study intervention.
[b] Mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity.
[c] Mild: 2.0 to ≤5.0 cm; moderate: 5.0 to ≤10.0 cm; severe: >10.0 cm.
[d] Any local reaction: any redness >2.0 cm, any swelling >2.0 cm, or any pain at the injection site.

Solicited systemic AEs

Among BNT162b2 recipients in both age groups, fatigue and headache were most common. The median onset of systemic events after either BNT162b2 dose occurred on Day 1 to Day 4, with resolution after a median duration of 1 day, except fatigue and chills which resolved within a median of 1-2 days. Solicited systemic AEs following both doses were mostly mild to moderate, and frequencies of severe systemic AEs, muscle pain, and joint pain were lower in participants 12-15 years of age than in those 16-25 years of age.

Within each age group, the frequency and severity of systemic AEs was higher after BNT162b2 Dose 2 than Dose 1, except for vomiting and diarrhea, which was generally similar for both doses.

Among 12-15-year-olds, systemic AEs were more frequently reported in BNT162b2 recipients than in the placebo group.

Table 17. Frequency of Solicited Systemic Adverse Events Within 7 Days After Each Dose, by Maximum Severity, Participants 12 Through 15 Years of Age and Participants 16 Through 25 Years of Age, Reactogenicity Subset[a]

Event	12-15 Years BNT162b2 Dose 1 N=1127 n (%)	12-15 Years Placebo Dose 1 N=1127 n (%)	12-15 Years BNT162b2 Dose 2 N=1097 n (%)	12-15 Years Placebo Dose 2 N=1078 n (%)	16-25 Years BNT162b2 Dose 1 N=531 n (%)	16-25 Years BNT162b2 Dose 2 N=488 n (%)
Fever						
≥38.0°C	114 (10.1)	12 (1.1)	215 (19.6)	7 (0.6)	39 (7.3)	84 (17.2)
≥38.0°C to 38.4°C	74 (6.6)	8 (0.7)	107 (9.8)	5 (0.5)	24 (4.5)	45 (9.2)
>38.4°C to 38.9°C	29 (2.6)	2 (0.2)	83 (7.6)	1 (0.1)	12 (2.3)	32 (6.6)
>38.9°C to 40.0°C	10 (0.9)	2 (0.2)	25 (2.3)	1 (0.1)	3 (0.6)	7 (1.4)
≥40.0°C	1 (0.1)	0	0	0	0	0
Fatigue[b]						
Any[e]	677 (60.1)	457 (40.6)	726 (66.2)	264 (24.5)	318 (59.9)	320 (65.6)
Mild	278 (24.7)	250 (22.2)	232 (21.1)	133 (12.3)	134 (25.2)	98 (20.1)
Moderate	384 (34.1)	199 (17.7)	468 (42.7)	127 (11.8)	173 (32.6)	199 (40.8)
Severe	15 (1.3)	8 (0.7)	26 (2.4)	4 (0.4)	11 (2.1)	23 (4.7)
Headache[b]						
Any[e]	623 (55.3)	396 (35.1)	708 (64.5)	263 (24.4)	286 (53.9)	297 (60.9)
Mild	361 (32.0)	256 (22.7)	302 (27.5)	169 (15.7)	151 (28.4)	119 (24.4)
Moderate	251 (22.3)	131 (11.6)	384 (35.0)	93 (8.6)	124 (23.4)	157 (32.2)
Severe	11 (1.0)	9 (0.8)	22 (2.0)	1 (0.1)	11 (2.1)	21 (4.3)
Chills[b]						
Any[e]	311 (27.6)	109 (9.7)	455 (41.5)	73 (6.8)	133 (25.0)	195 (40.0)
Mild	195 (17.3)	82 (7.3)	221 (20.1)	52 (4.8)	91 (17.1)	82 (16.8)
Moderate	111 (9.8)	25 (2.2)	214 (19.5)	21 (1.9)	37 (7.0)	101 (20.7)
Severe	5 (0.4)	2 (0.2)	20 (1.8)	0	5 (0.9)	12 (2.5)
Vomiting[c]						
Any[e]	31 (2.8)	10 (0.9)	29 (2.6)	12 (1.1)	9 (1.7)	13 (2.7)
Mild	30 (2.7)	8 (0.7)	25 (2.3)	11 (1.0)	9 (1.7)	10 (2.0)
Moderate	0	2 (0.2)	4 (0.4)	1 (0.1)	0	3 (0.6)
Severe	1 (0.1)	0	0	0	0	0
Diarrhea[d]						
Any[e]	90 (8.0)	82 (7.3)	65 (5.9)	43 (4.0)	57 (10.7)	39 (8.0)
Mild	77 (6.8)	72 (6.4)	59 (5.4)	38 (3.5)	50 (9.4)	32 (6.6)
Moderate	13 (1.2)	10 (0.9)	6 (0.5)	5 (0.5)	7 (1.3)	5 (1.0)
Severe	0	0	0	0	0	2 (0.4)
New or worsened muscle pain[a]						
Any[e]	272 (24.1)	148 (13.1)	355 (32.4)	90 (8.3)	143 (26.9)	199 (40.8)
Mild	125 (11.1)	88 (7.8)	152 (13.9)	51 (4.7)	67 (12.6)	93 (19.1)
Moderate	145 (12.9)	60 (5.3)	197 (18.0)	37 (3.4)	71 (13.4)	97 (19.9)
Severe	2 (0.2)	0	6 (0.5)	2 (0.2)	5 (0.9)	9 (1.8)
New or worsened joint pain[a]						
Any[e]	109 (9.7)	77 (6.8)	173 (15.8)	51 (4.7)	70 (13.2)	107 (21.9)
Mild	66 (5.9)	50 (4.4)	91 (8.3)	30 (2.8)	38 (7.2)	49 (10.0)
Moderate	42 (3.7)	27 (2.4)	78 (7.1)	21 (1.9)	29 (5.5)	54 (11.1)
Severe	1 (0.1)	0	4 (0.4)	0	3 (0.6)	4 (0.8)

Event	12-15 Years BNT162b2 Dose 1 N=1127 n (%)	12-15 Years Placebo Dose 1 N=1127 n (%)	12-15 Years BNT162b2 Dose 2 N=1097 n (%)	12-15 Years Placebo Dose 2 N=1078 n (%)	16-25 Years BNT162b2 Dose 1 N=531 n (%)	16-25 Years BNT162b2 Dose 2 N=488 n (%)
Use of antipyretic or pain medication[f]	413 (36.6)	111 (9.8)	557 (50.8)	95 (8.8)	167 (31.5)	223 (45.7)

Source: EUA 27034.132, c4591001--12-15-tables-figures.docx, Tables S and S.1, pages 20-22.
%:n/N. n=number of participants in the specified age group with the specified characteristic.
N=number of reactogenicity subset participants in the specified age group reporting at least 1 yes or no response for the specified reaction after the specified dose.
[a] All randomized participants in the reactogenicity subset who received at least 1 dose of the study intervention.
[b] Mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity.
[c] Mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration.
[d] Mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours.
[e] Any systemic event: any fever ≥38.0°C, any fatigue, any vomiting, any chills, any diarrhea, any headache, any new or worsened muscle pain, or any new or worsened joint pain.
[f] Severity was not collected for use of antipyretic or pain medication.

Subgroup analyses

Among 12-15-year-old BNT162b2 recipients, the frequencies of solicited local reactions and systemic AEs were generally similar among males and females.

Ethnicity: After Dose 2, Hispanic/Latino vaccine recipients reported notably lower rates for certain systemic AEs and higher rates for certain local reactions than non-Hispanic/non-Latino vaccine recipients.

- any fever: 9.4% (95%CI 4.9, 15.8) vs. 21.0% (95% CI 18.5, 23.7)
- any headache: 51.6% (95%CI 42.6, 60.5) vs. 66.3% (95% CI 63.2, 69.3)

These findings were accompanied by less antipyretic use after Dose 2 among Hispanic/Latino vaccine recipients compared with non-Hispanic/Latino vaccine recipients.

- any injection site swelling: 11.4% (95%CI 6.5, 18.0) vs. 4.7% (95% CI 3.4, 6.2)
- any injection site pain: 89.4% (95%CI 82.8, 94.1) vs. 79.1% (95% CI 76.4, 81.6)

Reactogenicity after Dose 1 was similar among Hispanic/Latino and non-Hispanic/non-Latino vaccine recipients.

The frequencies of solicited local reactions and systemic AEs were generally similar by race. While the proportions of African American, Asian and other racial groups in the study were reflective of the general distribution in the US population, the numbers of BNT162b2 recipients in these racial groups are too small (total n=157) to make definitive conclusions.

Reactogenicity in BNT162b2 recipients who were SARS-CoV-2 positive prior to Dose 1 (n=46) was similar to the overall population of vaccine recipients, but the number of subjects were too small to make definitive conclusions.

Unsolicited (non-serious and serious) AEs

Non-serious unsolicited AEs

Dose 1 through 1 month after Dose 2

Overall, among 12-15-year-olds, approximately 5.8% of participants in each treatment group (BNT162b2 and placebo) reported at least 1 non-serious AE from Dose 1 through 1 month after Dose 2 in ongoing follow-up. Differences in frequencies of AEs between the vaccine and placebo groups were notable for fever with onset within 7 days after vaccination and lymphadenopathy.

Reactogenicity

12-15-year-olds: 5 (0.4%) BNT162b2 recipients and 0 placebo recipients reported fever. AEs in the Medical Dictionary for Regulatory Activities System Organ Class (SOC) *General disorders and administration site conditions* were most frequently reported of all non-serious, unsolicited AEs in the BNT162b2 and placebo groups, of which injection site pain (0.6% BNT162b2, 0.6% placebo) and fatigue (0.6% BNT162b2, 0.4% placebo) were most common.

Comparator group of 16-25-year-olds (safety population): Approximately 50% of 16-25-year-olds were included in the reactogenicity subset, compared to 12-15-year-olds, who were all enrolled in the reactogenicity subset. Therefore, overall frequencies of reported unsolicited non-serious AEs in BNT162b2 recipients (27.9%) compared to placebo recipients (12.7%) were higher among 16-25-year-olds than 12-15-years-olds, primarily attributed to local and systemic adverse events reported during the first 7 days following vaccination and were consistent with adverse reactions/events solicited among participants in the reactogenicity subset.

Lymphadenopathy

12-15-year-olds: 7 (0.6%) BNT162b2 recipients and 1 (0.1%) placebo recipient reported lymphadenopathy; all of the events occurred within 2-10 days after study intervention, were located mainly in the arm/neck (axillary, cervical, supraclavicular lymph nodes), and were assessed as related to the study product by the investigator. In approximately 50% of participants, lymphadenopathy resolved within 1-10 days; in the remaining participants, the AE was ongoing at the time of data cutoff. Three additional reports of lymphadenopathy (2 BNT162b2 recipients and 1 placebo recipient) were assessed as unrelated by the study investigator due to onset ≥28 days after Dose 2 in the 2 BNT162b2 recipients and concurrent infectious mononucleosis in the placebo recipient. FDA agrees with the investigator's assessments.

Comparator group of 16-25-year-olds (safety population)*:* 7 (0.6%) BNT162b2 recipients reported lymphadenopathy, all plausibly related to vaccination, and no placebo recipients.

Hypersensitivity Reactions

12-15-year-olds: 6 BNT162b2 (0.53%) and 10 (0.89%) placebo recipients reported hypersensitivity-associated AEs, which were most frequently AEs included in the SOC *Skin and subcutaneous tissue disorders*; urticaria was most common in both study groups.

Comparator group of 16-25-year-olds (reactogenicity subset)*:* 6 BNT162b2 (1.12%) and 0 (0%) placebo recipients reported hypersensitivity-associated AEs, which were most frequently AEs included in the SOC *Skin and subcutaneous tissue disorders*; events categorized as 'rash' were most common.

Dose 1 to data cutoff date or participant's unblinding date (whichever was earlier)

12-15-year-olds: Other than lymphadenopathy, reactogenicity and hypersensitivity events reported from Dose 1 through 1 month after Dose 2, there were no other notable patterns between treatment groups for specific categories (SOC and Preferred Term (PT)) of non-serious adverse events, including Bell's palsy, facial paralysis/paresis, other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to BNT162b2 vaccine.

Comparator group of 16-25-year-olds (safety population): Unsolicited, non-serious AEs reported by 16-25-year-olds (from Dose 1 to the participant's unblinding date) are described in the Supplemental Safety Data section of this memo because their duration of safety follow-up was longer and thus more similar to that of the adult population than to that of 12-15-year-olds.

SAEs

Dose 1 through 1 month after Dose 2

12-15-year-olds: SAEs from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of BNT162b2 recipients and 0.1% of placebo recipients. A total of 5 SAEs were reported by 5 recipients (4 BNT162b2, 1 placebo), all who had no history of prior SARS-CoV-2 infection (SARS-CoV-2 negative at baseline).

BNT162b2:

- 3 participants, all with pre-existing anxiety and depression, were hospitalized for medical management of depression exacerbation that started 7 days after Dose 1, 1 day after Dose 2, and 15 days after Dose 1, respectively. All 3 participants reported treatment with a selective serotonin reuptake inhibitor (SSRI) that began within 1-2 months prior to vaccination. Worsening suicidal ideas with initial SSRI treatment in adolescents is a recognized risk and provides a reasonable alternative explanation for depression exacerbation in these BNT162b2 recipients.

- One participant experienced an SAE reported as generalized neuralgia, and also reported 3 concurrent non-serious AEs (abdominal pain, abscess, gastritis) and 1 concurrent SAE (constipation) within the same week. The participant was eventually diagnosed with functional abdominal pain. The event was reported as ongoing at the time of the cutoff date.

Placebo:

- One participant was hospitalized for appendicitis 19 days after Dose 2. The event resolved after 2 days and the participant continued in the study.

Comparator group of 16-25-year-olds (safety population): SAEs from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.3% of BNT162b2 recipients and 0.2% of placebo recipients. Six BNT162b2 recipients reported a total of 7 SAEs: concurrent

choledocholithiasis (1) and pancreatitis (1) in the same recipient; abdominal pain (1), appendicitis (1), deep vein thrombosis (DVT) (1), facial fracture (1), and osteochondritis (1). The DVT in the leg, which the study investigator attributed to a recent ankle fracture, occurred 19 days after BNT162b2 Dose 2. Clinical laboratory results were not provided. The event was ongoing at the time of the cut-off date. All SAEs in BNT162b2 recipients were considered unrelated to vaccination by the study investigator. No further information was provided by the Sponsor.

Four placebo recipients reported 4 SAEs: appendicitis (1), inguinal hernia (1), flail chest (associated with a motor vehicle accident) (1), and incomplete spontaneous abortion (1).

1 month after Dose 2 to data cutoff date or participant's unblinding date (whichever was earlier)

12-15-year-olds: A total of 3 SAEs from 1 month after Dose 2 in ongoing follow-up were reported in 3 recipients (2 BNT162b2, 1 placebo). All SAEs in BNT162b2 recipients were considered unrelated to vaccination by the study investigator and by FDA.

BNT162b2:

- 1 participant with constipation was diagnosed with functional abdominal pain after an extensive work-up; the participant also developed generalized neuralgia beginning 1 day after Dose 2 (described above).
- 1 participant with a long-standing history of ADHD and recent anxiety and depression diagnoses (4 months and 10 days prior to enrollment, respectively) was hospitalized for suicidal ideation 40 days after Dose 2. The event was ongoing at the time of the data cut-off date, but per the narrative provided by the Sponsor the event was assessed as resolved on March 15, 2021. The study investigator attributed the participant's symptoms to psychosocial issues expressed by the participant as the cause of her exacerbation.

Placebo:

- One participant was hospitalized for appendicitis 63 days after the Dose 2 of placebo. Symptoms were ongoing as of the data cutoff date.

Comparator group of 16-25-year-olds (safety population): Non-fatal SAEs described for 16-25-year-olds (from 1 month after Dose 2 to data cutoff or the participant's unblinding date, whichever was earlier) are described in the Supplemental Safety Data section of this memo because their duration of safety follow-up was longer and thus more similar to that of the adult population than to that of 12-15-year-olds.

Deaths

There were no deaths among participants 12-15 years of age or 16-25 years of age during the reporting period of Dose 1 to the data cutoff date.

AEs leading to study withdrawal

12-15-year-olds: 2 BNT162b2 recipients and no placebo recipients withdrew from the study due to an AE; one BNT162b2 recipient experienced fever (peak T40.3 ºC) [non-serious AE] starting 2 days after BNT162b2 Dose 1 and resolved after 2 days, and the other BNT162b2 recipient was hospitalized for exacerbation of pre-existing anxiety and depression (both SAEs; described above). The study investigator and FDA considered only the AE of fever to be related to vaccination.

Comparator group of 16-25-year-olds (safety population): please see Supplemental Safety Data section.

Pregnancies

12-15-year-olds: no pregnancies reported up to data cut-off of March 13, 2021.

Comparator group of 16-25-year-olds (safety population): 9 pregnancies (3 BNT162b2, 6 placebo) were reported through the cut-off date of March 13, 2021:

- BNT162b2 group: 1 pregnancy was ongoing at the time of data cut-off. For the other 2 participants, pregnancy exposure occurred >30 days after Dose 1; 1 participant discontinued from the study and the other participant was lost to follow-up.
- Placebo group: 3 pregnancies were ongoing at the time of data cut-off, and spontaneous abortion occurred in 1 participant. For the remaining 2 participants, pregnancy exposure occurred 11 days and 23 days, respectively, after placebo dose 1; both participants discontinued from the study. Additional information will be requested during the BLA review period.

Supplemental Safety Data

Participants 16-55 years of age: The Phase 2/3 safety population with data cut-off of March 13, 2021, consisted of 26,164 participants 16-55 years of age (13,069 BNT162b2 recipients, 13,095 placebo recipients); 82.5% of BNT162b2 recipients and 84.4% of placebo recipients had 2 to <6 months of follow-up after Dose 2; 10.4% of BNT162b2 recipients and 8.2% of placebo recipients had ≥6 months of follow-up after Dose 2. Follow-up time contributing to the supplemental safety data was limited to follow-up prior to unblinding of study participants and crossover of placebo recipients.

AEs of clinical interest

Dose 1 to participant's unblinding date

Non-serious AEs

- *Lymphadenopathy*: Among 16-55-year-olds, 67 BNT162b2 recipients and 4 placebo recipients reported lymphadenopathy, of which 3 BNT162b2 recipients reported lymphadenopathy after the EUA data cut-off date of November 14, 2020. Lymphadenopathy occurred within 2-4 days after vaccination (usually after Dose 2), was located in the arm/neck regions (i.e., axilla, cervical, supraclavicular), and resolved within approximately 1 week of onset, all which FDA considers plausibly related to vaccination.
- *Bell's Palsy/Facial Paralysis/Facial Paresis*: No additional cases were reported since those described in the original EUA.[1]
- *DVT*: 1 BNT162b2 recipient and 1 placebo recipient reported DVT that were characterized as non-serious AEs. The BNT162b2 recipient developed a DVT in the leg 14 days after Dose 2, resolved after 6 days, and assessed by the study investigator as unrelated to vaccination; no hematologic results or medical intervention details were provided. The placebo recipient developed a DVT in the leg 85 days after placebo dose 2 that resolved after 1 day and was attributed by the study investigator to metabolic causes. No further information was provided.

SAEs

- *Anaphylaxis:* No additional cases were reported from November 20, 2020 to March 13, 2021 cut-off date.
- *Appendicitis:* 13 BNT162b2 and 7 placebo recipients reported appendicitis, of which 5 occurred in each of the BNT162b2 and placebo groups after the EUA data cut-off date of November 14, 2020; overall, among 16-25-year-olds, 1 BNT162b2 recipient and 0 placebo recipients reported appendicitis. All of the participants reporting appendicitis recovered. At this time, there is no clear basis upon which to suspect that the imbalance among vaccine and placebo 16-55-year-olds represents a vaccine-related risk.
- *DVT:* A total of 7 participants (4 BNT162b2 recipients, 3 placebo recipients) reported 9 SAEs:
  - 2 BNT162 recipients reported a DVT (unspecified location [n=1], leg [n=1]) 11 days after Dose 1 and 19 days after Dose 2, respectively. The first participant consequently developed a pulmonary embolism (PE). The DVT and PE resolved; the study investigator attributed the DVT to the participant's pre-existing type 1 diabetes mellitus. For the second participant, the event was ongoing at the time of the data cut-off date (March 13, 2021); the study investigator attributed the DVT to a recent ankle fracture in the same limb. No further information was provided for either participant.
  - The remaining 5 participants (2 BNT162b2 recipients, 3 placebo recipients) developed DVTs 71-115 days after study intervention Dose 2. The 2 BNT162b2 recipients both reported DVTs in the legs bilaterally with consequent PEs; all events resolved and the causes of the DVTs are unknown. Two placebo recipients both reported DVTs in the leg, which the study investigator attributed to sport-related trauma and reduced mobility during quarantine, respectively; the event is ongoing for the first placebo recipient and resolved for the second placebo recipient. The third placebo recipient reported DVT in the arm, the cause is unknown, and the event was ongoing at the time of the data cut-off date. No hematologic results or treatment intervention information was provided for any of the 7 participants.

The clinical features of these thromboembolic SAEs do not appear to be similar to cases of thrombosis with thrombocytopenia syndrome (TTS) reported following adenovirus-vectored COVID-19 vaccines, and post-authorization surveillance of adverse events following >130 million doses of Pfizer-BioNTech COVID-19 Vaccine in individuals 16 years of age and older has not raised a signal for TTS.

Other non-serious, unsolicited AEs

Dose 1 through 30 days after Dose 2

As with the safety data submitted in support of the original EUA request (data cut-off of November 14, 2020), the overall frequency of unsolicited, non-serious adverse events through the data cut-off of March 13, 2021, was higher in the BNT162b2 group (24.0%) compared to placebo group (4.7%).This imbalance was primarily attributed to local reactions and systemic adverse events in participants not in the reactogenicity subset and consistent with solicited reactions/events reported by reactogenicity subset participants during the first 7 days following vaccination. No new imbalances were identified in frequencies of AEs from Dose 1 through 30 days after Dose 2 suggesting a causal relationship to BNT162b2, aside from previously identified imbalances in hypersensitivity reactions and Bell's palsy.

Dose 1 to participant's unblinding date

There were no newly identified notable patterns or numerical imbalances between treatment groups for specific categories (SOC and PT) of non-serious adverse events, including other neurologic, neuro-inflammatory events, that would suggest a causal relationship to BNT162b2 vaccine.

Other SAEs

Dose 1 through 30 days after Dose 2

Overall, the proportions of participants reporting at least 1 SAE in ongoing follow-up were the same in the BNT162b2 group (0.4%) as the placebo group (0.4%).

No additional SAEs in the BNT162b2 group considered related to vaccination by the study investigator were reported between the EUA data cutoff November 14, 2020 and March 13, 2021.

Dose 1 to participant's unblinding date

Eleven participants (3 BNT162b2 recipients, 8 placebo recipients) withdrew from the study due to at least 1 SAE: BNT162b2 group: lymphadenopathy (n=1), gastric adenocarcinoma (n=1), CNS metastases (n=1); placebo group: atrial fibrillation (n=1), visual impairment (n=1), diverticular perforation (n=1), drug overdose (n=1), amnesia (n=1), depression (n=1), suicide attempt (n=1), and respiratory arrest (n=1). Only the SAE of lymphadenopathy (reviewed under the original EUA request) was assessed by FDA as related to BNT162b2.[1]

There were 3 deaths in the BNT162b2 group and 4 deaths in the placebo group. The deaths in the vaccine group occurred at 86, 88, and 113 days after Dose 2, respectively, in participants who were 51-54 years of age; the listed causes of death (listed in the same order) were congestive heart failure, cardio-respiratory arrest and metastatic lung cancer. None of the reported deaths in BNT162b2 recipients were considered related to vaccination by the investigator or the FDA.

3.3 Data from Post-Authorization Safety Surveillance in Vaccine Participants 16 Years of Age and Older

As of April 20, 2021, 8,472 Pfizer-BioNTech COVID-19 Vaccine adverse event reports categorized as serious have been received and processed (coded, redacted, and quality assurance performed) by the Vaccine Adverse Event Reporting System (VAERS). The most common PTs among all VAERS reports are headache (n=9,126, 8.9%), chills (n=6,723, 6.6%), fatigue (n=6,720, 6.6%), pyrexia (6,565, 6.5%), pain (n=6,236, 6.1%), nausea (n=5,107, 5.0%), dizziness (n=4,671, 4.6%), pain in extremity (n=3,410, 3.3%), myalgia (n=3,225, 3.2%), and dyspnea (n=2,624, 2.6%). Other than anaphylaxis (discussed below), FDA review of VAERS reports, including serious and death reports, has not identified new safety concerns.

Data mining query with the Empirica Signal tool was performed on April 21, 2021 for each of the four Main Views (All Signals from Age Groups, All Signals from Gender, All Signals from Serious/Fatal, and All Signals from US/All VAERS). The data lock point was April 16, 2021. The alert score for disproportional reporting uses the lower bound of 95% confidence interval of

Empirical Bayesian geometric mean, EB05 >2.0. An EB05 of 2.064 was found for the PT 'Body Temperature' in adults ages 45-64.9 years of age. There were no other PTs with an EB05 >2.0.

Shortly after the issuance of the EUA, FDA received several reports of anaphylaxis following administration of the Pfizer-BioNTech COVID-19 Vaccine. Cases of anaphylaxis in the post-authorization experience are monitored by the Centers for Disease Control and Prevention (CDC) and FDA. Incoming VAERS reports are screened by CDC for potential cases of anaphylaxis. Additional clinical details are obtained by CDC staff by contacting the VAERS reporter and through review of medical records. Cases are classified as anaphylaxis using Brighton criteria. A case that meets the definition of Brighton Levels 1-3 is considered a case of anaphylaxis. Given the complexity of the Brighton criteria that require detailed clinical information, cases of anaphylaxis identified and classified by CDC are used. As of April 26, 2021, there have been 56 confirmed cases of anaphylaxis following the Pfizer-BioNTech COVID-19 Vaccine. Of the 56 cases, 51 (91.1%) are female and five (8.9%) are male. The median age is 39 years (range 27-67 years, unreported in one case). The time to onset from vaccination to the onset of symptoms of anaphylaxis ranged from immediately to 19 hours (unreported in three cases). Twenty-three (41.1%) cases met the criteria for Brighton Level 1, 30 (53.6%) were Brighton Level 2, and three (5.4%) were Brighton Level 3. As of April 26, 2021, a total of 120,774,248 doses of Pfizer-BioNTech COVID-19 Vaccine have been administered for an anaphylaxis reporting rate of 0.46 per million doses.

4. FDA Review of Other Information Submitted in Support of the EUA

4.1 Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

The Sponsor plans to offer vaccination to participants 12-15 years of age who originally received placebo and who are eligible for receipt of BNT162b2 according to local or national recommendations. The Sponsor proposes that these participants will be unblinded upon request and will have the opportunity to receive BNT162b2 as part of the study. The Sponsor also proposes that all participants ≥12 years of age who received placebo will be offered BNT162b2 after completing 6 months of follow-up after Dose 2 (if they have not already received it by this time). The participants will provide consent to receive vaccination and to continue follow-up. For these participants, the Sponsor plans a total follow-up period of 18 months, with a visit 1-month post-vaccination and subsequent phone contacts at 1, 6, and 18 months post-vaccination. Safety and efficacy monitoring during this period will include collection of AEs, SAEs, and screening and diagnosing COVID-19 cases.

4.2 Pharmacovigilance Activities

Pfizer submitted a revised Pharmacovigilance Plan to monitor safety concerns that could be associated with Pfizer-BioNTech COVID-19 Vaccine. The Sponsor includes anaphylaxis as an important identified risk. Vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease is included as an important potential risk. Use in pregnancy and lactation, vaccine effectiveness, and use in pediatric individuals <12 years of age are areas the Sponsor identified as missing information. Division of Epidemiology recommendations are as follows:

1. Mandatory reporting by the Sponsor of the following events to Vaccine Adverse Event Reporting System (VAERS) within 15 days:
    - SAEs (irrespective of attribution to vaccination)
    - Cases of multisystem inflammatory syndrome in children

- Cases of COVID-19 that result in hospitalization or death

2. The Sponsor will conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals. Each periodic safety report is required to contain descriptive information which includes:
   - A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and AESIs
   - A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval
   - Newly identified safety concerns in the interval
   - Actions taken since the last report because of adverse experiences (e.g., changes made to Fact Sheet for Vaccination Providers, changes made to studies or studies initiated)

3. The Sponsor will conduct one or more post-authorization observational studies to evaluate the association between BNT162b2 and a pre-specified list of AESIs, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized BNT162b2 under this EUA amendment to include individuals 12-15 years of age in the general U.S. population, populations of interest such as pregnant women, immunocompromised individuals, and subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. The Sponsor will provide protocols and status update reports with agreed-upon study designs and milestone dates. The Sponsor has proposed the following planned active surveillance study that will include adolescents ages 12-15 years:
   - Study Protocol Number C4591009. This is a post-approval observational study using real-world data to assess the association between the BNT162b2 and safety events of interest among persons administered the vaccine in the U.S. population and in populations of interest such as pregnant women, immunocompromised persons, and in persons with a prior history of COVID-19 infection. This study will use electronic health records and claims data from data partners participating in the Sentinel System (anticipated protocol submission: August 31, 2021).

     Of note, the Sponsor submitted a clinical study protocol to assess safety and immunogenicity in pregnant women and has proposed active surveillance studies designed to monitor pregnancy following administration of the vaccine within populations expected to receive the vaccine under EUA.

4. The Sponsor submitted a protocol for a vaccine effectiveness study:
   - Study Protocol Number C4591014. This study estimates vaccine effectiveness of two doses of the BNT162b2 in preventing hospitalization due to SARS-CoV-2 infection in individuals ≥16 years of age. Other objectives include evaluation of vaccine effectiveness after one dose, emergency department admission, specific variants, and other populations of interest. This study will utilize the Kaiser Permanente Southern California database. According to a response to an Information Request, the Sponsor plans to amend this protocol to include patients ages 12-15 years.

5. Active surveillance of vaccine recipients via the v-safe program: V-safe is a new smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The

system also will provide telephone follow-up to anyone who reports medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the participant received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate. V-safe may be modified to allow adolescents to self-register and report to v-safe, and a pathway created for a parent/guardian to report on behalf of younger children.

4.3 Chemistry, Manufacturing, and Control (CMC) Information

The Sponsor did not submit any new CMC information with this EUA amendment. Therefore, as determined during review of the original EUA request, the Pfizer-BioNTech COVID-19 Vaccine is manufactured with sufficient quality and consistency to support the proposed use under EUA.[1]

4.4 Clinical Assay Information

The SARS-CoV-2 mNG microneutralization assay measures neutralizing antibodies (50% inhibition titers) against SARS-CoV-2 using Vero cell monolayers in a 96-well plate format. The SARS-CoV-2 mNG virus is derived from the USA_WA1/2020 strain that had been rescued by reverse genetics and engineered to express a fluorescent reporter gene (mNeonGreen) upon productive infection of cells. The validation protocol (that includes evaluation of dilutional linearity, precision, limits of quantification, and limit of detection) and the results of the validation study, executed at Pfizer Hackensack Meridian Health Center (Nutley, New Jersey), were submitted to support the suitability of the assay for testing of clinical trial immunogenicity samples.

Two clinical diagnostic assays (Cepheid Xpert Xpress RT-PCR assay for the detection of SARS-CoV-2 in clinical specimens and Roche Elecsys Anti-SARS-CoV-2 assay for the evaluation of serostatus to SARS-CoV-2) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA. The Cepheid Xpert Xpress RT-PCR assay is used to assess viral infection of the subjects before vaccination and to confirm COVID-19 cases during study follow-up. The Roche Elecsys Anti-SARS-CoV-2 assay is used to assess serostatus of the subjects before vaccination. Data were submitted to support the suitability of both the Cepheid Xpert Xpress assay and the Roche Elecsys Anti-SARS-CoV-2 assay for their intended use in Phase 2/3 clinical studies when performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY).

4.5 Inspections of Clinical Study Sites

Bioresearch Monitoring inspections were conducted at three domestic clinical investigator sites participating in the conduct of study C4591001 that included pediatric subjects 12 through 15 years of age. Based on the review of the inspection reports, the inspections did not reveal problems impacting the data submitted in support of this EUA amendment.

4.6 EUA Prescribing Information and Fact Sheets

The Prescribing Information, Fact Sheet for Health Care Providers, and Fact Sheet for Participants were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

5. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

5.1 Known Benefits

The known benefit among participants of the Pfizer-BioNTech COVID-19 vaccine 12-15 years of age is reduction in the risk of confirmed COVID-19, relative to placebo, occurring at least 7 days after Dose 2, and reduction in the risk of confirmed COVID-19, relative to placebo, occurring between Dose 1 and 7 days after Dose 2 (with divergence of cumulative incidence of COVID-19 cases in BNT162b2 vs. placebo groups beginning at approximately 14 days after Dose 1).

Vaccine effectiveness in participants 12-15 years of age was inferred by immunobridging, based on a comparison of immune responses in participants 12-15 years of age with those of young adults 16-25 years of age (in whom VE has been demonstrated). The protocol-specified 2-dose vaccination regimen was also highly effective in preventing PCR-confirmed COVID-19 occurring at least 7 days after completion of the vaccination regimen in participants 12-15 years of age, which (although based on a small number of cases in descriptive analyses) provides compelling direct evidence of clinical benefit in addition to the immunobridging data.

5.2 Unknown Benefits/Data Gaps

The unknown benefits and data gaps associated with the Pfizer-BioNTech COVID-19 vaccine when used in adolescents 12-15 years of age are the same as those detailed in the memorandum authorizing the vaccine for emergency use in for the individuals 16 years of age and older.[1] They relate to:

- Duration of protection
- Effectiveness in certain populations at high risk of severe COVID-19
- Effectiveness in individuals previously infected with SARS-CoV-2
- Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections
- Vaccine effectiveness against asymptomatic infection
- Vaccine effectiveness against long-term effects of COVID-19 disease
- Vaccine effectiveness against mortality
- Vaccine effectiveness against transmission of SARS-CoV-2

This EUA Amendment provides additional insight for the following unknown benefit/data gap that was previously considered**:**

Effectiveness in pediatric populations

The study enrollment is limited to participants 12 years of age and older. No data are available at this time to evaluate the vaccine effectiveness in children under 12 years of age.

5.3 Known Risks

In individuals 12-15 years of age, there were higher frequencies of solicited local adverse reactions/systemic adverse events and lymphadenopathy in vaccine recipients than placebo recipients. Overall (after any dose), common solicited adverse reactions and events after BNT162b2 vaccination included injection site pain (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), all of which were generally mild to moderate and lasted a few days. Severe solicited local adverse reactions and systemic adverse events occurred in

0.0%-2.4% of 12-15-year-old BNT162b2 recipients; such events were more frequent after BNT162b2 Dose 2 than after BNT162b2 Dose 1 and more frequent in BNT162b2 recipients than age-matched placebo recipients. Among recipients of BNT162b2, severe solicited adverse reactions/events in 12-15-year-olds occurred less frequently than in 16-25-year-olds.

Among unsolicited adverse events reported from Dose 1 to 1 month after Dose 2, lymphadenopathy considered as related to study intervention by the study investigator and FDA occurred more frequently in the vaccine group (n=7) than the placebo group (n=1). The number of subjects reporting hypersensitivity-related adverse events was numerically lower in the vaccine group compared with the placebo group (6 [0.53%] vs. 10 [0.89%]).

Serious adverse events, while uncommon (<0.5%), represented medical events expected to occur among individuals in this age group and with the underlying conditions represented in the study population, and available data do not suggest a causal relationship to BNT162b2.

Although only 2 recipients (1 BNT162b2, 1 placebo) reported symptoms consistent with pre-syncope on the day of vaccination, vasovagal reactions are not uncommon in adolescents following vaccinations and other medical procedures involving needlesticks. The vaccine Fact Sheets and Prescribing Information for healthcare providers include a warning about measures to avoid injury following vasovagal/syncopal episodes in the immediate post-vaccination period.

Anaphylaxis, primarily among individuals with a history of severe allergic reactions to other medications or foods, has been documented to occur at a rate of 0.46 cases per million doses among vaccine recipients 16 years of age and older (similar to reported rates of anaphylaxis following licensed preventive vaccines). Risk of allergic reactions, including the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur and a contraindication for use in individuals with known allergy to any component of the vaccine, are described in the vaccine Fact Sheets and Prescribing Information. Additionally, risk of anaphylaxis/severe allergic reactions will be further evaluated as part of the pharmacovigilance plan for the vaccine.

5.4 Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 12 years of age, pregnant and lactating individuals, and immunocompromised individuals. Safety data in adolescents previously infected with SARS-CoV-2 are limited; however, re-infection has been documented and could be prevented by vaccination, and available data do not suggest safety concerns that would result in unfavorable benefit/risk in previously infected individuals.

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals 12-15 years of age may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of 3,769 participants described from Dose 1 through the data cutoff date (March 13, 2021). Active and passive safety surveillance will continue during the post authorization period to detect new safety signals.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

6. Overall Summary and Recommendation

Following review of information submitted in support of the EUA request, the review team concludes that:

- As summarized in Section 2 of this review, the CBRN agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials described in Section 3 of this review, the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) may be effective in preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2 in adolescents 12-15 years of age. Vaccine effectiveness was inferred by immunobridging based on a comparison of SARS-CoV-2 50% neutralization antibody titers at 1 month after Dose 2 in participants 12-15 years of age with those of young adults 16-25 years of age (the most clinically relevant subgroup of the study population in whom VE has been demonstrated). In the planned immunobridging analyses, the GMR of neutralizing antibody titers (adolescents to young adults) was 1.76 (95% CI: 1.47, 2.10), meeting the success criterion (lower bound of the 95% CI for the GMR >0.67). In a descriptive immunogenicity analysis, seroresponse rates among participants without prior evidence of SARS-CoV-2 infection were seen in 97.9% of adolescents and 100% of young adults (difference in seroconversion rates: -2.1%; 95% CI: -6.0%, 0.9%). Immunogenicity outcomes were consistent across demographic subgroups. In the supplemental efficacy analyses, VE after 7 days post Dose 2 was 100%, (95% CI 75.3; 100.0) in participants 12-15 years of age without prior evidence of SARS-CoV-2 infection and 100% in the group of participants with or without prior infection. VE between Dose 1 and Dose 2 was 75.0 (95% CI 7.4; 95.5), with divergence of cumulative incidence of COVID-19 cases in BNT162b2 vs. placebo groups beginning at approximately 14 days after Dose 1. Although based on a small number of cases in descriptive analyses, the supplementary VE data provide compelling direct evidence of clinical benefit in addition to the immunobridging data.

- Based on the data summarized in Sections 3 and 4 of this review and assessment of benefits and risks in Section 5 of this review, the known and potential benefits of the vaccine outweigh the known and potential risks of the vaccine when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12-15 years of age. Known benefits include reduction in the risk of confirmed COVID-19. Potential benefits that could be further evaluated but are not necessary to support an EUA include prevention of COVID-19 in individuals with previous SARS-CoV-2 infection, prevention of mortality and long-term complications of COVID-19, reduction in asymptomatic SARS-CoV-2 infection and reduction of SARS-CoV-2 transmission. Known risks include common local and systemic adverse reactions (notably injection site reactions, fatigue,

headache, chills, muscle pain, fever and joint pain), less commonly lymphadenopathy, and rarely anaphylaxis based on experience in Pfizer-BioNTech COVID-19 vaccine recipients 16 years of age and older with history of severe allergic reactions to other medications or foods. Potential risks that should be further evaluated include uncommon to rare clinically significant adverse reactions that may become apparent with more widespread use of the vaccine and with longer duration of follow-up, risks associated with vaccination of specific populations such as children younger than 12 years of age and pregnant and breastfeeding women, and whether vaccine-enhanced disease could occur with waning of immunity.

- As summarized in Section 2 of this review, there is no adequate, approved, or available alternative to the product to prevent COVID-19 caused by SARS-CoV-2 in individuals 12-15 years of age.

The review team therefore recommends issuance of an EUA for use of the Pfizer-BioNTech COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.

7. Appendix A. Charlson Comorbidity Index

This index is based on a list of 19 conditions identified from diagnoses in hospital and physician data. Each condition is assigned a weight from 1 to 6. The index score is the sum of the weights for all identified conditions (Charlson et al., 1987). An index score of 0 indicates no comorbid conditions, while higher scores indicate a greater level of comorbidity.

Charlson Index Diagnoses: Cancer, Chronic Pulmonary Disease, Diabetes without Complications, Congestive Heart Failure, Cerebrovascular Disease, Dementia, Renal Disease, Peripheral Vascular Disease, Myocardial Infarction, Diabetes with Complications, Paraplegia and Hemiplegia, Connective Tissue Disease-Rheumatic Disease, Peptic Ulcer Disease, Mild Liver Disease, Metastatic Carcinoma, Moderate or Severe Liver Disease, HIV/AIDS.

Source: Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–383. [PubMed: 3558716]

8. References

[1] FDA. Emergency Use Authorization Review Memorandum for the Pfizer-BioNTech COVID-19 Vaccine/ BNT162b2. December 11, 2020. https://www.fda.gov/media/144416/download

[2] Centers for Disease Control and Prevention, 2021. COVID Data Tracker (website) https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases and CDC communication

[3] Poline J, Gaschignard J, Leblanc C, et al. Systematic SARS-CoV-2 screening at hospital admission in children: a French prospective multicenter study. *Clin Infect Dis*. 2020 Jul 25:ciaa1044.

[4] Thompson MG, Burgess JL, Naleway AL, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021. *MMWR*. 2021;70(13):495-500.

[5] Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2021;175(2):143-156.

[6] Leidman E, Duca LM, Omura JD, et al. COVID-19 Trends Among Persons Aged 0-24 Years - United States, March 1-December 12, 2020. *MMWR*. 2021;70(3):88-94.

[7] Sargent TH, Muller WJ, Zheng X, et al. Age-Related Differences in Nasopharyngeal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Levels in Patients With Mild to Moderate Coronavirus Disease 2019 (COVID-19). *JAMA Pediatrics*. 2020;174(9):902-903.

[8] Yonker LM, Neilan AM, Bartsch Y, et al. Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Clinical Presentation, Infectivity, and Immune Responses. *J Pediatr*. 2020;227:45-52.e5.

[9] Centers for Disease Control and Prevention. Science Brief: Transmission of SARS-CoV-2 in K-12 schools. Updated March 19, 2021. https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/transmission_k_12_schools.html#sars-cov-2

[10] Goldstein E, Lipsitch M, Cevik M. On the Effect of Age on the Transmission of SARS-CoV-2 in Households, Schools, and the Community. *J Infect Dis*. 2021 Feb 13;223(3):362-369.

[11] Larosa E, Djuric O, Cassinadri M, et al. Secondary transmission of COVID-19 in preschool and school settings in northern Italy after their reopening in September 2020: a population-based study. *Euro Surveill.* 2020;25(49):2001911.

[12] Kim L, Whitaker M, O'Halloran A, et al. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 – COVID-NET, 14 States, March 1-July 25, 2020. *MMWR*. 2020;69(32):1081-1088.

[13] Centers For Disease Control and Prevention. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). February 17, 2021. https://www.cdc.gov/mis-c/hcp/

[14] Centers for Disease Control and Prevention. Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States. April 1, 2021. https://www.cdc.gov/mis-c/cases/index.html

[15] Racine N, Cooke JE, Eirich R, Korczak DJ, McArthur B, Madigan S. Child and adolescent mental illness during COVID-19: A rapid review. *Psychiatry Res*. 2020;292:113307.

[16] Magson NR, Freeman JYA, Rapee RM, Richardson CE, Oar EL, Fardouly J. Risk and Protective Factors for Prospective Changes in Adolescent Mental Health during the COVID-19 Pandemic. *J Youth Adolesc*. 2021 Jan;50(1):44-57.

[17] Hill RM, Rufino K, Kurian S, et al. Suicide Ideation and Attempts in a Pediatric Emergency Department Before and During COVID-19. *Pediatrics*. 2021 Mar;147(3):e2020029280.

[18] Thompson MG, Burgess JL, Naleway AL, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March 2021. *MMWR*. 2021;70(13):495-500.

[19] Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med*. 2021 Apr 15;384(15):1412-1423.

[20] FDA. Emergency Use Authorization 091 casirivimab and imdevimab. February 25, 2021. https://www.fda.gov/media/145610/download

[21] FDA. Emergency Use Authorization 094 bamlanivimab and etesevimab. February 25, 2021. https://www.fda.gov/media/145801/download

[22] Centers for Disease Control and Prevention, 2021, COVID-19 Breakthrough Case Investigations and Reporting. accessed May 4,2021. https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html

[23] Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb–3 and 360bbb-3b. (2011)

[24] FDA. Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19. February 2021. https://www.fda.gov/media/142749/download

[25] FDA. Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19